Exhibit 93, part 6

4.2 Mechanisms of carcinogenicity

It is generally accepted that alveolar macrophages and neutrophils play a central role in diseases associated with exposure to crystalline silica (Hamilton *et al.*, 2008). An inflammation-based mechanism as described in IARC (1997) is a likely mechanism responsible for the induction of lung cancer associated with exposure to crystalline silica, although reactive oxygen species can be directly generated by crystalline silica polymorphs themselves, and can be taken up by epithelial cells. For this reason, a direct effect on lung epithelial cells cannot be excluded (Schins, 2002; Fubini & Hubbard, 2003; Knaapen *et al.* 2004).

4.2.1 Physicochemical features of crystalline silica dusts associated with carcinogenicity

The major forms or polymorphs of crystalline silica are the natural minerals quartz, tridymite, cristobalite, coesite, stishovite, and the artifical silica-based zeolites (porosils) (Fenoglio *et al.*, 2000a). Humans have been exposed only to quartz, tridymite, cristobalite, the other forms being very rare. Several amorphous forms of silica exist, some of which were classified in Group 3 (*not classifiable as to their carcinogenicity*) in the previous *IARC Monograph* (IARC, 1997). Also, it has been shown that this cytotoxicity is lowered with lowering hydrophilicity (Fubini *et al.*, 1999), which depends upon the circumstances under which the surface was created. For example, silica in fly ashes or volcanic dusts is generated at high temperatures, and is mostly hydrophobic.

The classification in Group 1 (*carcinogenic to humans*) of some silica polymorphs in the previous *IARC Monograph* (IARC, 1997) was preceded by a preamble indicating that crystalline silica did not show the same carcinogenic potency in all circumstances. Physicochemical features – polymorph characteristics, associated contaminants – may account for the differences found in humans and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called "variability of quartz hazard" have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle (Donaldson & Borm, 1998; Fubini, 1998a; Elias *et al.*, 2000; Donaldson *et al.*, 2001). The larger potency of freshly ground dusts (e.g. as in sandblasting) has been confirmed in several studies; Vallyathan *et al.*, 1995), as immediately after cleavage, a large number of surface-active radicals are formed that rapidly decay (Damm & Peukert, 2009). The association with clay or other aluminium-containing compounds inhibits most adverse effects (Duffin *et al.*, 2001; Schins *et al.*, 2002a), iron in traces may enhance the effects but an iron coverage inhibits cytotoxicity and cell transformation (Fubini *et al.*, 2001). One study on a large variety of commercial quartz dusts has shown a spectrum of variability in oxidative stress and inflammogenicity *in vitro* and *in vivo*, which exceeds the differences previously found among different polymorphs (Bruch *et al.*, 2004; Cakmak *et al.*, 2004; Fubini *et al.*, 2004; Seiler *et al.*, 2004). Subtle differences in the level of contaminants appear to determine such variability. New studies *in vitro* and *in vivo* on synthesized nanoparticles of quartz (Warheit *et al.*, 2007) indicate a variability of effects also at the nanoscale. These new data clearly show that more or less pathogenic materials are comprised under the term "crystalline silica dusts." However, most studies, so far, have failed to identify strict criteria to distinguish between potentially more or less hazardous forms of crystalline silica.

The pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the

grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron) (Fubini *et al.*, 2004).

The toxicity of silica dust from various sources may be related either to the kind of silica polymorph or to impurities.

The correlation between artificially pure crystalline silicas (porosils) with similar physicochemical properties, but different micromorphology, size and surface area, was investigated (Fenoglio *et al.*, 2000a). Surface area and aspect ratio (elongated crystals with a higher aspect ratio than more isometric crystals) of the particulates tested in a cellular system (mouse monocyte-macrophage tumour cell line) correlate best with inhibition of cell proliferation after 24–72 hours experimental time. From the natural crystalline silicas, only stishovite did not show a cytotoxic effect; all the other natural polymorphs were rather toxic. Stishovite is made up of smooth round particles (Cerrato *et al.*, 1995) whereas quartz, tridymite, and cristobalite consist of particles with very sharp edges caused by grinding (Fubini, 1998a; Fubini *et al.*, 1990, 1999). Stishovite, the only polymorph with silicon in octahedral coordination, has densely packed hydroxyl-silanols on its surface that interact with hydrogen bonds with each other; for this reason, the interaction of silanols with cell membranes, which normally does occur, is dramatically reduced (Cerrato *et al.*, 1995).

Pure silica-zeolites with different particle forms exhibit similar cytotoxicity *in vitro* if compared at equal surface area instead of equal mass. The extent of free radical generation did not show a significant correlation with cytotoxicity in this short-term in-vitro test (Fenoglio *et al.*, 2000a). Free radicals generated by the particle may play a role in later stages of toxicity related to crystalline silica (Ziemann *et al.*, 2009). Both silicon-based surface radicals and iron ions located at the particle surface may be active centres for free radical release in solution (Fubini *et al.*, 2001).

As has already been demonstrated with quartz and cristobalite (Brown & Donaldson, 1996; Bégin *et al.*, 1987), the cytotoxicity of artificially pure silica-zeolites can be decreased by aluminium ions adsorbed onto the particle surface (Fenoglio *et al.*, 2000a). Crystalline silica may occur naturally embedded in clays or may be mixed with other materials in some commercial products. It is possible that these materials may adsorb onto the silica surface, and modify its reactivity. However, the extent of surface coverage and the potency of these modified crystalline silica particles after long-term residence in the lungs have not been systematically assessed.

A quartz sample isolated from bentonite clay obtained from a 100 to 112 million-year-old formation in Wyoming, USA, exhibits a low degree of internal crystal organization, and the surface of this quartz particles are occluded by coatings of the clay. This "quartz isolate" was compared in respect to its toxic potency after intratracheal instillation in rats with the quartz sample DQ12. The "quartz isolate" showed a much lower toxicity than DQ12 quartz, in agreement with the much lower surface reactivity of "quartz isolate" compared to the DQ12 quartz (Creutzenberg *et al.*, 2008; Miles *et al.*, 2008).

4.2.2 Direct genotoxicity and cell transformation

Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic and epithelial cells exposed to quartz particles (Castranova *et al.*, 1991; Deshpande *et al.*, 2002). Oxidants generated by silica particles and by the respiratory burst of silica-activated phagocytic cells may cause cellular and lung injury, including DNA damage. Lung injury may be initiated and amplified by severe inflammation (Donaldson *et al.*, 2001; Castranova, 2004; Knaapen *et al.*, 2004). Various

products (chemotactic factors, cytokines, growth factors) released by activated (and also dying) alveolar macrophages will not only recruit more macrophages as well as polymorphonuclear leukocytes (PMNs) and lymphocytes, but may also affect and activate bronchiolar and alveolar epithelial cells.

Reactive oxygen species can directly induce DNA damage (Knaapen *et al.*, 2002; Schins *et al.*, 2002b), and morphological transformations observed in Syrian hamster embryo (SHE) cells correlate well with the amount of hydroxyl radicals generated (Elias *et al.*, 2000, 2006; Fubini *et al.*, 2001). Neoplastic transformation was observed in in-vitro assays in the absence of secondary inflammatory cells (Hersterberg *et al.*, 1986; Saffiotti & Ahmed, 1995; Elias *et al.*, 2000). There seems to be no correlation between the extent of cytotoxicity as assessed by colony-forming efficiency and transforming potency (SHE test) when various quartz samples were investigated (Elias *et al.*, 2000). In contrast to transforming potency, which was clearly related to hydroxyl radical generation, cytotoxicity was not affected by antioxidants. Partial reduction of transforming potency when deferoxamine-treated quartz was used points to the role of transitional metals, e.g. iron on the particle surface in generating hydroxyl radicals (Fubini *et al.*, 2001). The SHE test used in this study by Fubini *et al.* (2001) and by others is recommended by the Centre for the Validation of Alternative Methods (ECVAM) as an alternative method for investigating the potential carcinogenicity of particulates (Fubini, 1998b). In nude mice injected with these transformed cells, tumours could be initiated (Saffiotti & Ahmed, 1995).

Particle uptake by target cells is also relevant for direct genotoxicity (Schins, 2002). Crystalline silica particles were detected in type II lung epithelial cells (RLE-6TN) *in vitro*; these particles were located also in close proximity to the nuclei and mitochondria, but not within these organelles. An osteosarcoma cell line lacking functional mitochondria was investigated with respect to quartz-related DNA damage with an osteosarcoma cell line with normal mitochondria. Only the cell line with functioning mitochondria showed significantly increased DNA damage after exposure to DQ12 quartz (Li *et al.*, 2007).

The relationship between genotoxic effects (formation of DNA strand breaks) and the uptake of quartz particles was investigated *in vitro* with A549 human lung epithelial cells (Schins *et al.*, 2002a). The percentage of A549 cells containing particles was clearly lower after exposure to quartz coated with polyvinylpynidine-*N*-oxide or aluminum lactate compared to uncoated quartz (DQ12). In this experiment, DNA strand breaks measured (Comet assay) in the exposed cells correlated very well with the number of particles absorbed by the cells. It could also be demonstrated that the generation of reactive oxygen species was closely related to the formation of DNA strand breaks (Schins, 2002). However, in other in-vitro studies using different quartz species, DNA strand breaks in epithelial cells could be observed only at particle concentrations that caused cytotoxicity (Cakmak *et al.*, 2004).

Rats were exposed to crystalline silica for 3 hours and sacrificed at different time points after exposure, and lungs were examined by electron microscopy. The lungs were fixed by vascular perfusion through the right ventricle. In these investigations, silica crystals were found within the cytoplasm of type I lung epithelial cells (Brody *et al.*, 1982). Although type I cells are not the target cell for tumour formation, these data show that the uptake of quartz particles in epithelial lung cells *in vivo* is in principle possible. Other particles including titanium dioxide, carbon black, or metallic particles have occasionally been found in type I lung epithelial cells in rats after inhalation exposure (Anttila, 1986; Anttila *et al.*, 1988; Nolte *et al.*, 1994).

After intratracheal instillation of DQ12 quartz, DNA strand breaks could be observed in lung epithelial cells isolated from quartz-treated rats. This effect was not found when the quartz dust was treated with either polyvinylpyridine-*N*-oxide or aluminium lactate. This finding suggests an important role of the reactive surface of quartz-induced DNA damage *in vivo*. No increase in alkaline phosphatase was found in the bronchiolo-alveolar lavage fluid of quartz-treated rats, and therefore, as alkaline phosphatase is an enzyme specifically present in type II epithelial cells, it can be assumed that there was no obvious cytotoxicity in these lung cells. These data support the current view of the important role of inflammatory cells in quartz-induced genotoxic effects (Knaapen *et al.*, 2002).

4.2.3 Depletion of antioxidant defences

Substantial amounts of ascorbic acid (Fenoglio *et al.*, 2000b) and glutathione (Fenoglio *et al.*, 2003) are consumed in the presence of quartz in cell-free tests via two different surface reactions. Both reactions may deplete antioxidant defences in the lung-lining fluid, thereby enhancing the extent of oxidative damage.

Incubation of murine alveolar MH-S macrophages with quartz particles (80 µg/cm^2) for 24 hours inhibited glucose 6-phosphate dehydrogenase (G6PD)-1 activity by 70%, and the pentose phosphate pathway by 30%. Such effects were accompanied by a 50% decrease in intracellular glutathione. Quartz inhibits G6PD but not other oxidoreductases, and this inhibition is prevented by glutathione, suggesting that silica contributes to oxidative stress also by inhibiting the pentose phosphate pathway, which is critical for the regeneration of reduced glutathione (Polimeni *et al.*, 2008).

4.2.4 Indirect mechanisms

After 13 weeks of inhalation exposure to 3 mg/m^3 crystalline silica (mass median aerodynamic diameter, 1.3 µm) or 50 mg/m^3 amorphous silica (mass median aerodynamic diameter, 0.81 µm), the percentage of PMNs in the lung of the exposed rats was similar after each exposure. However, HPRT mutation frequency of the alveolar epithelial cells was significantly increased only in rats exposed to crystalline silica. Other factors including toxic effects to epithelial cells, solubility, and biopersistence may also be important for the induction of these mutagenic effects (Johnston *et al.*, 2000). A specific finding in rats treated intratracheally with amorphous silica (Aerosil®150, pyrogenic silica with primary particle size of 14 nm) was a severe granulomatous alveolitis which over time progressed to "scar-like" interstitial fibrotic granulomas not seen after crystalline silica exposure in rats (Ernst *et al.*, 2002). Lung tumours were found in rats also after the repeated intratracheal instillation of the same amorphous silica (Kolling *et al.*, 2008).

Toxic mineral dusts, especially crystalline silica, have unique, potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (silicosis) and lung cancer (Hamilton *et al.*, 2008). Macrophages express a variety of cell-surface receptors that bind to mineral dusts leading to phagocytosis, macrophage apoptosis, or macrophage activation. The major macrophage receptor that recognizes and binds inhaled particles as well as unopsonized bacteria is MARCO (Arredouani *et al.*, 2004, 2005). Additional members of the macrophage-scavenger receptor family responsible for binding mineral particles as well as a wide range of other ligands include SR-AI and SR-AII (Murphy *et al.*, 2005). Although SR-AI/II and MARCO bind both toxic and non-toxic particles, only crystalline silica triggers macrophage apoptosis following

binding to these scavenger receptors (Hamilton *et al.*, 2008). Other receptors expressed by macrophages and other target cells in the lung that bind mineral dusts include complement receptor and mannose receptors (Gordon, 2002). The pathological consequences of silica-induced injury to alveolar macrophages followed by apoptosis is impaired alveolar-macrophage-mediated clearance of crystalline silica as discussed in Section 4.1. Lysosomal membrane permeabilization following phagocytosis of crystalline silica particles has been hypothesized to enhance IL-1β secretion (Hornung *et al.*, 2008), and to trigger the release of cathepsin D, leading to mitochondrial damage, and the apoptosis of alveolar macrophages (Thibodeau *et al.*, 2004). Macrophage injury and apoptosis may be responsible for the increased susceptibility of workers exposed to silica to develop autoimmune disease (Pfau *et al.*, 2004; Brown *et al.*, 2005), and pulmonary tuberculosis (IARC, 1997; Huaux, 2007).

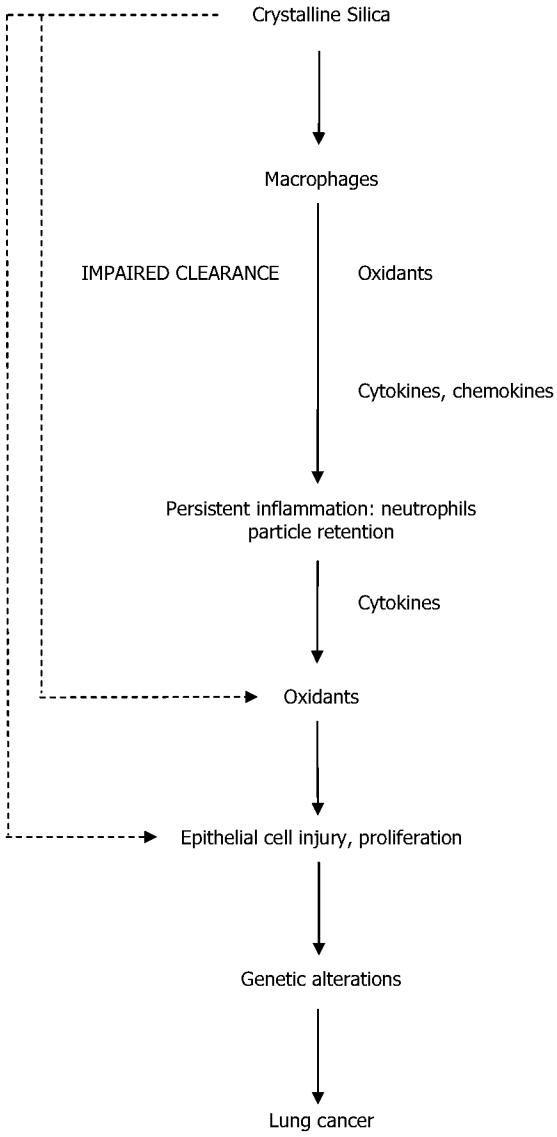
Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats, see Fig. 4.1 (IARC, 1997). Rats exposed to crystalline silica develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumours (Driscoll *et al.*, 1997). These persistent inflammatory and epithelial proliferative responses are less intense in mice and hamsters, and these species do not develop lung tumours following exposure to crystalline silica or other poorly soluble particles (IARC, 1997). There has been considerable discussion of whether the response of rats to inhaled particles is an appropriate model for the exposed response of humans (ILSI, 2000). Comparative histopathological studies of rats and humans exposed to the same particulate stimuli reveal more severe inflammation, alveolar lipoproteinosis, and alveolar epithelial hyperplasia in rats than in humans (Green *et al.*, 2007). These studies suggest that rats are more susceptible to develop persistent lung inflammation in response to particle inhalation than other species (ILSI, 2000).

Chronic exposure of rats to crystalline silica also leads to pulmonary fibrosis (Oberdörster, 1996), and workers with silicosis have an elevated risk of developing lung cancer (Pelucchi *et al.*, 2006). The causal association between chronic inflammation, fibrosis, and lung cancer was reviewed by IARC (2002). These associations provide a biological plausible mechanism between inflammation and the development of fibrosis and/or lung cancer (Balkwill & Mantovani, 2001).

4.3 Molecular pathogenesis of cancer of the lung

Acquired molecular alterations in oncogenes and tumour-suppressor genes characterize the multistage development of lung cancer (Sato *et al.*, 2007). Somatic alterations, such as DNA adducts, develop in the respiratory tract of smokers during the early stages of carcinogenesis (Wiencke *et al.*, 1999). Specific point mutations in in the *K-RAS* oncogene and the *p53* tumour-suppressor gene are considered as biomarkers of exposure to chemical carcinogens in tobacco smoke (Pfeifer *et al.*, 2002). Only one study has investigated the mutational spectrum of these genes that may be used as biomarkers for exposure to crystalline silica. Liu *et al.* (2000) analysed the mutation spectra in the *K-RAS* and *p53* genes in lung cancers that developed in workers with silicosis [smoking status unknown]. In a series of 36 cases, 16 mutations in exons 5, 7 and 8 of the *p53* gene were found. In contrast to non-occupational lung cancers, seven of these mutations clustered in exon 8. Most of the *K-RAS* gene mutations in non-small cell lung carcinomas occur at codon 12. Liu *et al.* (2000) did not detect this mutation in their case series of silicotics. Six mutations were found at codon 15 in exon 1 as well as additional mutations in codons 7, 15, 20, and

Fig. 4.1 Proposed mechanisms for the carcinogenicity of crystalline silica in rats



21. Most of these mutations were G→C transversions in contrast to G→T transversions at codon 12, which are characteristic of non-small cell lung cancers associated with tobacco smoking. If these specific mutations are confirmed in a larger series of lung cancers in silicotics, these could provide early biomarkers for the development of lung cancer in workers exposed to crystalline silica.

In a rat model of silica-induced lung cancer, a low frequency of *p53* gene mutations and no mutations in *K-RAS, N-RAS,* or *c-H-RAS* oncogenes were observed (Blanco *et al.*, 2007). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to crystalline silica.

The epigenetic silencing of the $p16^{INK4a}$ (Belinsky *et al.*, 2002), *CDH13,* and *APC* genes has also been found in a rat model of lung cancer induced by intratracheal instillation of crystalline silica (Blanco *et al.*, 2007). In this rodent model, the increased expression of iNOS

(inducible nitric oxide synthase) was also found in preneoplastic lesions, which is consistent with a role for reactive nitrogen species in silicosis (Porter *et al.*, 2006).

4.4 Species differences and susceptible populations

In rat chronic inhalation studies using crystalline silica or granular, poorly soluble particles, female rats are more susceptible than males to the induction of lung tumours. Overall, rats are susceptible to the induction of lung cancer following the exposure to crystalline silica or granular, poorly soluble particles, but hamsters and mice are more resistant. The mechanistic basis for these sex and species differences is unknown. Mice exposed to crystalline silica by intranasal instillation or subcutaneous injection, as well as rats injected intrapleurally or intraperitoneally develop lymphomas. Following inhalation exposure to crystalline silica, lymphomas have not been observed in any species (see Section 3).

In some workers exposed to crystalline silica, cytokine gene polymorphisms have been linked with silicosis (Yucesoy *et al.*, 2002). Specific polymorphisms in genes encoding in *TNF-α* and *IL-1RA* (interleukin-1 receptor antagonist) have been associated with an increased risk for the development of silicosis (Yucesoy & Luster, 2007). Gene–linkage analyses might reveal additional markers for susceptibility to the development of silicosis and lung cancer in workers exposed to crystalline silica.

4.5 Synthesis

Three mechanisms have been proposed for the carcinogenicity of crystalline silica in rats (Fig. 4.1). First, exposure to crystalline silica impairs alveolar-macrophage-mediated particle clearance thereby increasing persistence of silica in the lungs, which results in macrophage activation, and the sustained release of chemokines and cytokines. In rats, persistent inflammation is characterized by neutrophils that generate oxidants that induce genotoxicity, injury, and proliferation of lung epithelial cells leading to the development of lung cancer. Second, extracellular generation of free radicals by crystalline silica depletes antioxidants in the lung-lining fluid, and induces epithelial cell injury followed by epithelial cell proliferation. Third, crystalline silica particles are taken up by epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity.

The Working Group considers the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The mechanism responsible for the induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of quartz dust.

There is *limited evidence* in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.

Crystalline silica in the form of quartz or cristobalite dust is *carcinogenic to humans (Group 1).*

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WOOD DUST

Wood dust was considered by a previous IARC Working Group in 1994 (IARC, 1995), although wood-related occupations (i.e. Furniture and Cabinet-making) had been considered by IARC Working Groups earlier, in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification, chemical, and physical properties of the agent

Wood dust, generated in the processing of wood for a wide range of uses, is a complex substance. Its composition varies considerably according to the species of tree being processed. Wood dust is composed mainly of cellulose (approximately 40–50%), polyoses, lignin, and a large and variable number of substances of lower relative molecular mass which may significantly affect the properties of the wood. These include non-polar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerides), polar organic extractives (tannins, flavonoids, quinones, and lignans) and water-soluble extractives (carbohydrates, alkaloids, proteins, and inorganic material) (IARC, 1995).

Trees are characterized botanically as gymnosperms (principally conifers, generally referred to as 'softwoods'), and angiosperms (principally deciduous trees, generally referred to as 'hardwoods'). Softwood and hardwood are not botanical concepts, referring to the species of tree and not directly describing the hardness of wood. Out of 12000 different species of trees, only about 800 are coniferous or softwoods, but roughly two-thirds of the wood used commercially worldwide belongs to the group of softwoods. Hardwoods tend to be somewhat more dense, and have a higher content of polar extractives than softwoods (IARC, 1995). For a comparison of softwoods and hardwoods, see Table 1.1.

For detailed descriptions of the classification and nomenclature, anatomical features, cell-wall structures, distribution of components of wood, and chemical components of wood, see the previous *IARC Monograph* (IARC, 1995), Nimz *et al.* (2005), and Kretschmann *et al.* (2007).

1.2 Occupational exposure

The wood species used in wood-related industries vary greatly by region and by type of product. Both hardwoods and softwoods (either domestically grown or imported) are used in the manufacture of furniture. Logging, sawmills, plywood, and particle-board manufacture generally involve the use of trees grown locally (IARC,

Table 1.1 Comparison of softwoods and hardwoods

Characteristic	Gymnosperms/conifers/softwoods	Angiosperms/deciduous wood/ hardwoods
Density (g/cm^3)	White (silver) fir: mean, 0.41 (0.32–0.71) European spruce: mean, 0.43 (0.30–0.64) Scots pine: mean, 0.49 (0.30–0.86)	European beech 0.68 (0.49–0.88) European oak 0.65 (0.39–0.93)
Fibres	Long (1.4–4.4 mm)	Short (0.2–2.4 mm)
Cell type	One (tracheids)	Various
Cellulose	~40–50%	~40–50%
Unit	β-D-Glucose	β-D-Glucose
Fibre pulp	Long	Short
Polyoses	~15–30%	~25–35%
Unit	More mannose More galactose	More xylose
Lignin	~25–35%	~20–30%
Unit	Mainly guaiacyl	Mainly syringyl or guaiacyl
Methoxy group content	~15%	~20%
Extractive content		
Non-polar (e.g. terpenes)	High	Low
Polar (e.g. tannins)	Low	High

Reprinted in part from Volume 62 (IARC, 1995)

1995). For detailed descriptions of historical exposures to wood dust and other agents in the workplace, see the previous *IARC Monograph* (IARC, 1995).

1.2.1 Extent of occupational exposure

Kauppinen *et al.* (2006) used nearly 36000 exposure measurements to estimate the occupational exposure to inhalable wood dust by country, industry, the level of exposure and type of wood dust in 25 Member States of the European Union. In 2000–03, approximately 3.6 million workers in the European Union [and undoubtedly millions more worldwide] were exposed occupationally to inhalable wood dust. The estimated number of workers exposed by industry and the number exposed to a level exceeding 5 mg/m^3 are shown in Table 1.2. The highest exposure levels were estimated to occur in the construction sector and furniture industry. Due to limited exposure data, there was considerable uncertainty in the estimates concerning construction woodworkers. About 560000 workers (16% of the number of workers exposed) may have been exposed to a level of inhalable wood dust that exceeded 5 mg/m^3. Mixed exposures to more than one species of wood and dust from wooden boards was very common, but reliable data on exposure to different species of wood could not be retrieved.

The US National Occupational Exposure Survey, carried out during 1981–83 in the United States of America, estimated that about 600000 workers were exposed to wood dust. The largest numbers of exposed workers were employed in the building trades (n = 134090), and the lumber/wood product industries (n = 153543). Forestry workers (e.g. lumberjacks using chainsaws) were not considered to be exposed in this survey (NIOSH, 1990).

Table 1.2 WOODEX: Estimated number of workers exposed to wood dust in the 25 Member States of the European Union, 2000–03

Industry	Number employed	Number exposed	Exposed (% of employed)	Number exposed > 5 mg/m^3
Construction	13 million	1.2 million	9	254000
Manufacture of furniture	1.2 million	713000	59	86500
Manufacture of joinery	472000	330000	71	42000
Forestry	445000	148000	33	< 100
Building of ships and boats	294000	31000	11	9600
Sawmilling	259000	196000	76	20000
Manufacture of other wood products	147000	97000	66	15500
Manufacture of wooden boards	124000	92000	74	8400
Manufacture of wooden containers	80000	57000	71	8600
All other employment	163 million	709000	0.4	118000
Total	179 million	3.6 million	2.0	563000

From Kauppinen *et al.* (2006)

1.2.2 Levels of occupational exposure

The highest exposures to wood dust have generally been reported in wood furniture and cabinet manufacture, especially during machine-sanding and similar operations (with wood dust levels frequently above 5 mg/m^3). Exposure levels above 1 mg/m^3 have also been measured in the finishing departments of plywood and particle-board mills, where wood is sawn and sanded, and in the workroom air of sawmills and planer mills near chippers, saws, and planers. Exposure to wood dust also occurs among workers in joinery shops, window and door manufacture, wooden boat manufacture, installation and refinishing of wood floors, pattern and model making, pulp and paper manufacture, construction carpentry, and logging. Measurements are generally available only since the 1970s, and exposures may have been higher in the past because of less efficient (or non-existent) local exhaust ventilation or other measures to control dust (IARC, 1995).

Woodworking machines have increased greatly in efficiency since the industrial revolution, and the increased speed of production has resulted in the generation of more dust. The increased efficiency may also result in exposure to finer wood dust particles than in the past, because smoother surfaces can be produced, and because saws and bits may retain their sharpness for longer. The introduction of engineering controls in some industries in some parts of the world, especially since the 1950s, has, however, reduced the exposure of workers considerably. Unfortunately, engineering controls, even if properly maintained, are not always effective, and the dust generated by hand-held power tools, particularly sanders, is much more difficult to control (IARC, 1995).

Studies published since the previous *IARC Monograph* reporting wood dust concentrations are presented in Table 1.3.

1.2.3 Particle size distribution

Chung *et al.* (2000) characterized the quantity, particle size distribution and morphology of dust created during the machining of medium-density fibreboard (MDF) in a controlled environment (a 2 × 2 × 2 m^3 dust chamber). In terms of particle size distribution and morphology, the dust generated by machining MDF was generally found to be comparable with the dust generated by similarly machining hardwood or softwood. The quantity of dust generated during sanding

Table 1.3 Wood dust concentrations in various industries around the world

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
Sawmills and lumber mills				
Demers *et al.* (2000), Teschke *et al.* (1999b) Softwood lumber mill British Columbia, Canada July–August 1996	Sawmill, planer mill, and yard	*Geometric mean (GSD)* Inhalable particulate: 1.0 (2.7) Estimated wood dust: 0.5 (3.1)	220	Exposure assessment conducted for cross-sectional study of respiratory health among 275 softwood lumber mill workers; mill processed spruce (*Picea engelmannii* and *glauca*), pine (*Pinus contorta*), and fir (*Abies lasiocarpa*); random sampling strategy; full-shift (7–8 hours) personal inhalable particulate samples collected using seven-hole inhalable dust samplers; wood dust exposure estimated using the resin acid content within dust in combination with observations of job tasks, proximity to dust sources and use of personal protective equipment
Rosenberg *et al.* (2002) Sawmill, Finland 1997–99	Sawhouse - pine processing - spruce processing	*Range of geometric means* Inhalable particulate: 0.5–2.2 Inhalable particulate: 0.4–1.9	237 (178 personal)	Measured exposure of 22 sawhouse workers in mills processing pine (*Pinus silvestris*) and spruce (*Picea abies*); full-shift area and personal inhalable particulate samples collected in breathing zone; exposure measured during evening shift on three consecutive days; IOM samplers to collect inhalable dust; gravimetric determination of inhalable dust; assumption that all or most of inhalable dust originated from wood dust
Hall *et al.* (2002), Sawmills British Columbia, Canada 1981–97	Lumber mill	*Geometric mean (GSD)* 0.72 (3.49)	1237	Analysis of compliance data set (and a nested subset of research data) containing personal exposure measurements to wood dust at 77 lumber mills; 23% of database were research samples, 77% were compliance samples; an empirical "determinants of exposure" model created using multiple linear regression

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
Rusca *et al.* (2008), Sawmill Switzerland June–October 2002	Sawmill	*Mean (range)* Inhalable particulate: 1.7 (0.2–8.5)	NR	Cross-sectional survey of male employees at 12 sawmills processing spruce and fir species in the French part of Switzerland; personal measurements of inhalable dust collected using IOM samplers; gravimetric analysis of inhalable dust
Miscellaneous wood-related occupations				
Edman *et al.* (2003) Wood pellets and briquettes Sweden	Industrial production of wood pellets and briquettes	*Geometric mean (range)* overall: 1.7 (0.16–19)	24	Personal exposure to wood dust measured gravimetrically and with personal data logging, real-time aerosol monitor; sampling time: 8 hours;
Kalliny *et al.* (2008) Wood-processing plants USA 1999–2004	Sawmill, plywood assembly plants, secondary wood milling operations, factories producing finished wood products	*Geometric mean (GSD)* Inhalable: 1.44 (2.67) Thoracic: 0.35 (2.65) Respirable: 0.18 (2.54)		Size-fractionated dust exposure surveyed longitudinally in 10 wood processing plants across the USA; dust exposures measured using the RespiCon Personal Particle Sampler; woods processed included softwoods (e.g. southern yellow pine and Radiata pine), hardwoods (red oak, maple, poplar, birch, rubber tree wood, cherry), engineered woods (medium-density fibreboard, particleboard), and plywood (from southern yellow pine)
Teschke *et al.* (1999a) Misc. establishments USA 1979–97	Overall	*Geometric mean (GSD)* 1.86 (6.82)	1632 personal TWA samples	Analysis of 1632 measurements of airborne wood dust reported to OSHA's Integrated Management Information System and development of an empirical predictive model; measurements collected using OSHA sampling method for "total" particulate (i.e. non-specific gravimetric method)
	Sanders, transportation equipment industry	17.5 (1.79)		
	Press operators, wood products industry	12.3 (4.12)		
	Lathe operators, furniture industry	7.46 (4.56)		
	Sanders, wood cabinet industry	5.83 (5.19)		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
Commonwealth of Australia (2008) Wood industries Australia	All wood industries	*Arithmetic mean (range)* 5.8 (0.06–210)	521	Analysis of existing surveillance data on inhalable wood dust exposure; data gathered via a review of published Australian literature; requests to government agencies, consultants, industry associations, specific industries and researchers; telephone surveys, and new air sampling
Alwis *et al.* (1999); Mandryk *et al.* (1999) Wood industries New South Wales, Australia 1996–97		*Geometric mean (GSD)* Inhalable dust		Personal inhalable and respirable samples collected; sampling time: 6–8 hours
	Logging	0.6 (1.3)	7	
	Sawmill	1.6 (3.2)	93	
	Wood chipping	1.9 (1.7)	9	
	Joinery	3.7 (3.7)	66	
		Respirable dust		
	Logging	< 0.1 (1.3)	4	
	Sawmill	0.3 (2.2)	31	
	Wood chipping	0.3 (1.7)	4	
	Joinery	0.5 (1.7)	39	
Scarselli *et al.* (2008) Wood industries Italy 1996–2006	All wood-related	*Geometric mean (GSD)* 1.0 (1.6)	10837	Analysis of airborne wood dust exposure measurements contained in the SIREP (Italian Information System on Occupational Exposure to Carcinogens) database; 10837 measurements on 10528 workers at 1181 companies; concentration of wood dust (hardwood or mixed wood dust) measured as 8-h TWA; no information about type of sample (personal vs stationary) or sampling strategy (random vs systematic)
Baran & Teul (2007) Wood processing Poland	Sawmill, manufacturing frames for furniture, and manufacturing ready-made furniture	*Range* 0.59–16.2		Analysis of measurements on 1100 workers employed in 9 wood-processing plants: 2 sawmills, 4 plants manufacturing frames for upholstered furniture, and 3 plants manufacturing ready-made furniture

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
HSE (2000); Black *et al.* (2007) Woodworking United Kingdom 1999–2000	Sawmilling, joinery, furniture manufacture, other	*Range of medians* 1.5–2.8	396	Cross-sectional survey of 46 representative companies in the British woodworking industry; personal samples collected as per MDHS 14/3; sampling time: 3–6 hours during activities judged to be representative of whole shift; gravimetric analysis of inhalable dust
Spee *et al.* (2007) Building projects the Netherlands 2002	Carpenters	*Geometric mean (GSD)*		Task-based exposure survey of 26 carpenters at 13 building projects from 12 companies; personal and area samples randomly collected as per specially designed protocol for sampling of wood dust in carpentry and furniture industry; gravimetric analysis of wood dust
	- overall	3.3 (2.1)	44	
	Task-based	*Arithmetic mean*		
	- working indoors	5.2	29	
	- working outdoors	2.2	11	
	- indoors + outdoors	16.2	4	

GSD, geometric standard deviation; NR, not reported; OSHA, Occupational Safety and Health Administration; TWA, time-weighted average

was higher for sanding MDF when compared with sanding either hardwood or softwood. However, there was no significant difference with sanding MDF and natural woods, in terms of the quantity of dust generated.

Additional information on the particle size distribution of wood dust in workroom air can be found in the previous *IARC Monograph* (IARC, 1995).

1.2.4 Exposure to other agents

Within the furniture-manufacturing industry, exposure may occur to solvents and formaldehyde in glues and surface coatings. Such exposures are usually greatest for workers with low or negligible exposure to wood dust, and are infrequent or low for workers with high exposure to wood dust. Some outdoor furniture has also been manufactured from impregnated wood containing copper–chromium–arsenic compounds. Formaldehyde-based glues and varnishes were introduced in the wood industry after World War II but they became commonly used only in the 1950s and 1960s in most countries.

The manufacture of plywood and particle board may result in exposure to formaldehyde, solvents, phenol, wood preservatives, and engine exhausts. Sawmill workers may also be exposed to wood preservatives and fungal spores. Wood preservatives used include chlorophenol salts in sawmills, and organochlorine pesticides in plywood mills. When coniferous trees are sawn, monoterpenes evaporate into workroom air. In some sawmills, wood is also impregnated with copper–chromium–arsenic salts or creosote. Construction woodworkers may be exposed to asbestos and silica in their work environment. Many of them also varnish wooden floors with solvent- or water-based varnishes, some of which may release formaldehyde. Exposures to chemicals in industries where other wood products are manufactured vary, but are in many cases similar to those in the furniture-manufacturing industry (IARC, 1995).

1.2.5 Exposure of the general population

Woodworking is a popular hobby and non-occupational exposure may also occur during building and repair operations in homes. Woodworking can encompass a variety of activities that generate wood dust, including sawing, sanding, planing, routing, etc. The woods worked include a variety of particle boards, soft timbers, treated pine, masonite, plywood, and various imported hardwoods and softwoods. The size of the dust particles produced, the amount of dust, and resultant exposure to the person working in these areas depends on several factors including the equipment being used, the ventilation and extraction system in place, the state and type of timber, the general ventilation in the area, and any personal protective equipment that may be used. Exposure levels during non-occupational woodworking may be similar to those at workplaces, but the duration of exposure is usually substantially shorter.

2. Cancer in Humans

In the previous *IARC Monograph*, the evidence associated with exposure to wood dust or wood-related occupations or activites and cancer of the nasal cavity and paranasal sinuses (referred to below as 'sinonasal cancer'), and of the nasopharynx, larynx, lung, stomach, colon, and rectum as well as leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma was systematically reviewed because excesses had been observed in one or more studies. The Working Group for the previous *IARC Monograph* concluded that there was very strong evidence for sinonasal cancer. In case–control studies, they also consistently observed associations between exposure to wood

dust and cancer of the nasopharynx, but could not rule out confounding; and between wood dust and cancer of the larynx, but noted conflicting evidence from cohort studies. The Working Group concluded that there was "no indication that occupational exposure to wood dust has a causal role in cancers of the oropharynx, hypopharynx, lung, lymphatic and haematopoietic systems, stomach, colon, or rectum" (IARC, 1995).

Since the previous *IARC Monograph*, several studies have been published including selected case series of sinonasal cancer (see Table 2.1), cohort studies (see Table 2.2), registry-based studies (see Table 2.3). For case–control or other studies focused on particular cancer sites, only studies published since the previous volume that reported results for wood dust exposure are summarized here. The results of case–control studies on sinonasal, pharyngeal, and laryngeal cancer are summarized in Tables 2.4, 2.5, and 2.6, respectively. In addition, the results of case–control studies on lung cancer are summarized in Table 2.7, because of the relatively large number of studies that focus on this cancer site. Studies of other cancer sites are summarized in Table 2.8.

2.1 Sinonasal cancer

The Working Group for the previous *IARC Monograph* (IARC, 1995) reviewed a large number of case–control studies that consistently observed a strong association between exposure to wood dust or employment in wood-related occupations and sinonasal cancer. Support for this association was found in several large cohort studies of furniture workers (Olsen & Sabroe, 1979; Acheson *et al.*, 1984), but most cohort studies had little power to examine the risks for this cancer site (see Table 18, IARC, 1995). Odds ratios for all or unspecified sinonasal cancers were consistently elevated in case–control studies conducted in many countries (see Table 20, IARC, 1995).

Very high odds ratios were observed for sinonasal adenocarcinoma and strong evidence of a exposure–response relationship was observed in some studies (Hayes *et al.*, 1986; Olsen & Asnaes, 1986; Luce *et al.*, 1993) (see Table 21, IARC, 1995). In addition, an unusually large proportion of all adenocarcinomas in cases series were woodworkers. Some case–control studies observed an excess risk of sinonasal squamous cell carcinoma associated with wood dust or wood occupations, but the association was much weaker than was observed with adenocarcinoma (see Table 22, IARC, 1995). A pooled re-analysis of 12 case–control studies (including six of the nine above) found strong evidence for a exposure–response relationship among men for adenocarcinoma (OR, 0.6; 95%CI: 0.6–4.7 for low; OR, 3.1; 95%CI: 1.6–6.1 for moderate; and OR, 45.5; 95%CI: 28.3–72.9 for high wood dust), and little evidence for squamous cell carcinoma (OR, 0.9; 95%CI: 0.6–1.2 for low; OR, 1.0; 95%CI: 0.7–1.4 for moderate; and OR, 0.8; 95%CI: 0.4–1.6 for high wood dust) (Demers *et al.*, 1995a). For the three studies with results for squamous cell carcinoma not included in the pooled re-analysis, Fukuda *et al.* (1987) observed an excess among both male (OR, 2.9; 95%CI: 1.5–5.6) and female woodworkers (OR, 2.0; 95%CI: 0.3–14), Shimizu *et al.* (1989) observed an excess of squamous cell carcinoma of the maxillary sinus among male woodworkers (OR, 2.1; 95%CI: 0.8–5.3), and Olsen & Asnaes (1986) observed only a slightly increased risk of carcinoma of the sinonasal cavities among men classified as exposed to wood dust (OR, 1.3; 95%CI: 0.6–2.8).

Among the cohort studies that reported tree species, an excess of sinonasal cancer (SMR, 8.1; 95%CI: 3.7–16) was observed among British furniture workers exposed to hardwood dust (Rang & Acheson, 1981; Acheson *et al.*, 1984). No cases of sinonasal cancer were reported in a much smaller study of German furniture

workers exposed to beech, oak, and pine (Barthel & Dietrich, 1989) or among two small cohort of workers exposed to softwood—Finnish sawmill workers (Jäppinen *et al.*, 1989) and American plywood workers (Robinson *et al.*, 1990). [The Working Group noted that their power to detect an excess was low, and that exposure levels among sawmill and plywood workers were low compared to furniture workers.]

Few case–control studies in the previous *IARC Monograph* reported tree species. Very large excesses of sinonasal adenocarcinoma were associated with hardwood dust exposure in studies from France (OR, 5.30; 95%CI: 1.04–2.70, for highest level of exposure, Leclerc *et al.*, 1994) and Italy (OR, 0.90; 95%CI: 0.20–4.07, Battista *et al.*, 1983). Excesses of sinonasal cancer were observed among workers primarily exposed to softwood in case–control studies from Nordic Countries (OR, 3.3; 95%CI: 1.1–9.4, Hernberg *et al.*, 1983), the USA (OR, 3.1; 95%CI: 1.0–9.0 with 15-year lag, Vaughan *et al.*, 2000), Canada (OR, 2.5; $P < 0.03$, Elwood, 1981), and France (OR, 1.7, Leclerc *et al.*, 1994). The results for three of these four studies were restricted to squamous cell carcinoma.

Early case series reported many cases of sinonasal adenocarcinoma that were exposed to hardwoods (Acheson *et al.*, 1968, 1972; Leroux-Robert, 1974; Luboinski & Marandas, 1975; Andersen *et al.*, 1976, 1977; Engzell *et al.*, 1978; Kleinsasser & Schroeder, 1989). Seven cases of sinonasal squamous cell carcinoma exposed to "softwoods" were reported in a Norwegian case series (Voss *et al.*, 1985), and three cases of adenocarcinoma were reported among British workers exposed to softwoods (Acheson *et al.*, 1972). Several new case series have also been published with results relevant for the evaluation of sinonasal cancer (Table 2.1). Case series of sinonasal adenocarcinoma continue to make up a large proportion of cases with exposure to wood dust, with mean exposure durations ranging from 25 to 37 years. Most case series were restricted to adenocarcinoma, but in the case series that considered other tumours, the proportion of wood dust exposure was much less in the non-adenocarcinoma cases.

In the period following the previous *IARC Monograph* (IARC, 1995), five cohort studies (Table 2.2) were published that are relevant for the evaluation of wood dust, and three present results for sinonasal cancer. In a pooled re-analysis of five previously published cohort studies, Demers *et al.* (1995b) found an excess risk of sinonasal cancer among men classified as being definitely exposed to wood dust (SMR, 8.4; 95%CI: 3.9–16.0). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. Innos *et al.* (2000) found an excess risk of sinonasal cancer among Estonian furniture workers highly exposed to wood dust (for men SIR, 2.3; 95%CI: 0.3–8.4, $n = 2$; for women SIR, 3.2; 95%CI: 0.1–18.1, $n = 1$).

Three new case–control studies (Table 2.4) have published results relevant for the evaluation of sinonasal cancer. Teschke *et al.* (1997) found no association with softwood or hardwood dust in a small Canadian study. In a pooled re-analysis of European case–control studies 't Mannetje *et al.* (1999) found a strong association with adenocarcinoma (OR, 12.2; 95%CI: 7.4–20.0), but no association with squamous cell carcinoma (OR, 0.7; 95%CI: 0.5–1.1). Pesch *et al.* (2008) found a strong association between adenocarcinoma and hardwood dust exposure (OR, 4.0; 95%CI: 1.9–8.3), but not with softwood dust exposure (OR, 0.3; 95%CI: 0.2–0.7). [The Working Group noted that only compensated cases were included, and this may have biased the results towards hardwood dust exposure.]

Table 2.1 Case series of sinonasal cancer according to occupation and exposure to wood dust

Reference, location, name of study	Sex	Origin	Histology	Exposed cases/ total cases	Occupations/exposures	Comments
Svane-Knudsen *et al.* (1998) Denmark	M, F	Nasal cavity and paranasal sinuses Hospital-based series 1978–95	Adenocarcinomas Epidermoid carcinomas	12/22 3/41	Hardwood dust exposure based on patient records [further details were not provided]	Softwood dust exposure not mentioned
Stoll *et al.* (2001) France	M, F	Ethmoidal sinuses 1975–2000	Adenocarcinomas	62/76	Exposed to wood dust	Mean duration of wood dust exposure 26 yr
Roux *et al.* (2002) France		Sinonasal cancer 1985–2001	Adenocarcinomas	134/139	Wood dust exposure from furniture, sawmill, carpentry and wood-product workers	Mean duration of wood dust exposure 30 yr
Barbieri *et al.* (2005) Italy	M, F	Ethmoidal sinuses 1978–2002	Adenocarcinomas	17/100	Hardwood and softwood dust exposure (5 softwood only)	
Liétin *et al.* (2006) France	M, F	Ethmoidal sinuses Hospital-based series 1985–2004	Adenocarcinomas	45/60	Wood dust exposure	Mean duration of wood dust exposure 25.6, range 2–44 yr
Fontana *et al.* (2008) France	M, F	Sinonasal cancer Diagnostic Registry 1981–2000	All	46/76 men 0/24 women	Wood dust exposure	Mean duration of wood dust exposure 37 yr
Llorente *et al.* (2008) Spain	M, F	Hospital-based series 1986–2002	All	62/79	Wood dust exposure	
Bornholdt *et al.* (2008) Denmark	M, F	Sinonasal cancer 1991–2001	Adenocarcinomas Squamous cell carcinomas	33/58 7/109	Wood dust exposure as per job title from the Central Person Registry or interview	
Choussy *et al.* (2008) France	M, F	Ethmoidal sinuses Hospital-based series 1976–2001	Adenocarcinomas	353/418	Wood dust exposure	Mean duration of wood dust exposure 27.7 yr

Table 2.2 Cohort studies of woodworkers exposed to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) Cohort mortality study United Kingdom and USA	Pooled analysis of updated data from 5 studies: British furniture workers (Acheson *et al.*, 1984), US furniture workers (Miller *et al.*, 1994), two cohorts of plywood workers (Blair *et al.*, 1990; Robinson *et al.*, 1995), and wood model makers (Roscoe *et al.*, 1992)	Workers classified as exposed to wood dust based on available work history	All cancers (140–208)	All woodworkers	1726	0.8 (0.8–0.8)	SMRs adjusted for sex, age, & calendar period using national rates	
			Pharynx (146–149)	All woodworkers	20	0.8 (0.5–1.3)		
			Nasopharynx (147)	All woodworkers	9	2.4 (1.1–4.5)		
				Possible wood dust	4	2.9 (0.8–7.5)		
				Probable wood dust	0	0.0 (0.0–3.8)		
				Definite wood dust	5	5.3 (1.7–12.4)		
			Paranasal sinus (160)	All woodworkers	11	3.1 (1.6–5.6)		
				Possible wood dust	1	0.8 (0.0–4.6)		
				Probable wood dust	1	1.2 (0.0–6.5)		
				Definite wood dust	9	8.4 (3.9–16.)		
			Larynx (161)	All woodworkers	18	0.7 (0.4–1.0)		
				Possible wood dust	4	0.4 (0.1–1.1)		
				Probable wood dust	8	1.1 (0.5–2.1)		
				Definite wood dust	6	0.8 (0.3–1.8)		
			Lung (162)	All woodworkers	575	0.8 (0.7–0.9)		
			Stomach (151)	All woodworkers	138	0.9 (0.8–1.1)		
			Intestine (152, 153)	All woodworkers	136	0.8 (0.6–0.9)		
			Rectum (154)	All woodworkers	60	0.8 (0.6–1.0)		
			Non-Hodgkin lymphoma (200, 202)	All woodworkers	57	1.1 (0.8–1.4)		
			Hodgkin disease (201)	All woodworkers	12	0.6 (0.3–1.1)		
			Multiple myeloma (203)	All woodworkers	33	1.3 (0.9–1.3)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) (contd.)				Possible wood dust	9	1.0 (0.5–1.9)		
				Probable wood dust	8	1.3 (0.6–2.5)		
				Definite wood dust	11	1.6 (0.8–2.8)		
			Leukaemia (204–208)	All woodworkers	47	0.7 (0.5–0.9)		
Stellman *et al.* (1998) Prospective cohort USA	Prospective study of 362823 men enrolled in the American Cancer Society Cancer Prevention Study II in 1982 and followed up for 6 yr	Self-reported wood dust exposure or wood-related occupation	All causes (0–999)	Wood dust exposure	2995	1.1 (1.0–1.1)	RRs adjusted for age and smoking status	
				Wood occupation	1271	1.2 (1.1–1.2)		
			All cancers (140–208)	Wood dust exposure	961	1.1 (1.0–1.2)		
				Wood occupation	381	1.2 (1.1–1.3)		
			Pharynx (146–149)	Wood dust exposure	7	0.9 (0.4–2.0)		
				Wood occupation	2	0.8 (0.2–3.4)		
			Nasopharynx (147)	Wood dust exposure	1	0.4 (0.1–3.3)		
				Wood occupation	1	1.4 (0.4–1.8)		
			Paranasal sinus (160)	Wood dust exposure	1	1.1 (0.1–8.4)		
				Wood occupation	0			
			Larynx (161)	Wood dust exposure	8	1.6 (0.8–3.4)		
				Wood occupation	2	1.2 (0.3–4.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
(Stellman *et al.* (1998) contd.)			Lung (162)	Wood dust exposure	317	1.2 (1.0–1.3)		
				Wood occupation	111	1.1 (0.9–1.4)		
			Stomach (151)	Wood dust exposure	40	1.3 (1.0–1.9)		
				Wood occupation	11	1.1 (0.6–1.9)		
			Colon (153)	Wood dust exposure	100	1.0 (0.8–1.3)		
				Wood occupation	37	1.0 (0.8–1.5)		
			Rectum (154)	Wood dust exposure	23	1.3 (0.8–2.0)		
				Wood occupation	9	1.5 (0.8–2.9)		
			Non-Hodgkin lymphoma (200, 202)	Wood dust exposure	39	1.1 (0.8–1.5)		
				Wood occupation	12	1.0 (0.6–1.7)		
			Hodgkin disease (201)	Wood dust exposure	4	1.2 (0.4–3.4)		
				Wood occupation	1	1.0 (0.1–7.7)		
			Multiple myeloma (203)	Wood dust exposure	16	1.0 (0.6–1.8)		
				Wood occupation	4	0.7 (0.3–1.9)		
			Leukaemia (204–208)	Wood dust exposure	32	0.9 (0.6–1.3)		
				Wood occupation	14	1.1 (0.6–1.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) Retrospective cancer incidence cohort study Estonia	Retrospective study of incident cancers in all furniture workers employed in Tallinn, Estonia, for at least six months between 1 January 1946 and 31 December 1988 and living in Estonia on 1 January 1968. Cancer incidence follow-up: 1968–95	Exposure based on industrial hygiene surveys and work history	All cancers (140–208)	Med. exposure men	55	1.2 (0.9–1.6)	SIRs adjusted for age and calendar period	
				High exposure men	265	1.0 (0.9–1.1)		
				Med. exposure women	98	1.0 (0.8–1.2)		
				High exposure women	171	1.1 (0.9–1.3)		
			Buccal cavity (140–145)	Med. exposure men	5	3.7 (1.2–8.6)		
				High exposure Men	6	0.8 (0.3–1.7)		
				Med. exposure women	2	2.5 (0.3–8.9)		
				High exposure women	2	1.6 (0.2–5.8)		
			Pharynx (146–149)	Med. exposure men	3	4.0 (0.8–11.8)		
				High exposure men	6	1.5 (0.6–3.3)		
				Med. exposure women	0	0.0		
				High exposure women	0	0.0		
			Paranasal sinus (160)	Med. exposure men	0	0.0		
				High exposure men	2	2.3 (0.3–8.4)		
				Med exposure women	0	0.0		
				High exposure women	1	3.2 (0.1–18.1)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Larynx	Men	7	0.7 (0.3–1.4)		
				Women	1	1.7 (0.0–9.4)		
			Bronchi and lung (162)	Med. exposure men	9	0.8 (0.4–1.5)		
				High exposure men	70	1.0 (0.8–1.3)		
				Med. exposure women	5	1.1 (0.4–2.6)		
				High exposure women	11	1.6 (0.8–2.9)		
			Stomach (151)	Med. exposure men	11	1.7 (0.9–3.0)		
				High exposure men	36	0.9 (0.6–1.2)		
				Med. exposure women	13	1.2 (0.7–2.1)		
				High exposure women	23	1.4 (0.9–2.1		
			Colon (153)	Med. exposure men	6	3.0 (1.1–6.7)		
				High exposure men	18	1.5 (0.9–2.4)		
				Med. exposure women	8	1.4 (0.6–2.7)		
				High exposure women	16	1.8 (1.0–2.9)		
			Rectum (154)	Med. exposure men	1	0.6 (0.0–3.2)		
				High exposure men	13	1.2 (0.7–2.1)		
				Med. exposure women	7	1.6 (0.6–3.2)		
				High exposure women	11	1.6 (0.8–2.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Hodgkin disease (201)	Med. exposure men	1	2.6 (0.1–14.3)		
				High exposure men	3	1.4 (0.3–4.2)		
				Med. exposure Women	0	0.0		
				High exposure women	1	1.3 (0.0–7.5)		
			Haematopoietic and lymphatic (200–208)	Med. exposure men	2	0.8 (0.1–2.8)		
				High exposure men	14	0.9 (0.5–1.5)		
				Med. exposure women	5	1.0 (0.3–2.3)		
				High exposure women	3	0.4 (0.1–1.2)		
Szadkowska-Stańczyk & Szymczak (2001) Nested case–control study Poland	79 deceased lung cancer cases from a cohort of 10575 Polish pulp and paper mill workers (7084 men, 3491 women), 1+ yr, 1968–90, observed through 1995	Employment history obtained from the mills; occupational exposure was assessed by experts and a cumulative dose index	Lung (162)	Wood dust exposure	10	2.1 (0.9–4.9)	ORs adjusted for smoking. Matched on sex, birth year (± 1 yr), hire year (± 3 yr), and vital status	
				Low	4	2.1 (0.6–7.4)		
				Moderate & high	6	2.1 (0.7–6.3)		
				1–4 yr of exposure	4	1.7 (0.5–6.2)		
				5+ yr of exposure	6	2.4 (0.8–7.7)		
				Low cumulative dose	4	2.1 (0.5–9.2)		
				High cumulative dose	6	2.0 (0.7–5.4)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (2003) Cohort mortality study USA	13354 male carpenter members of the United Brotherhood of Carpenters and Joiners of America matched to the New Jersey State Cancer registry, who had participated in the New Jersey Carpenters fund before 1 July 2000 and matched to the New Jersey Carpenters Pension Fund All incident cancer cases within the cohort 1979–2000	Employment as a carpenter	All cancers (140–208)	All	592	1.1 (1.0–1.2)	SIRs adjusted for age and calendar period	The lowest duration of carpenter work (< 10 yr) was used as the comparison group for expected cases
			Pharynx (146–149)		11	1.4 (0.7–2.4)		
			Oesophagus (150)		8	1.1 (0.5–2.2)		
			Stomach (151)		12	1.0 (0.5–1.8)		
			Rectum (154)		35	1.5 (1.1–2.1)		
			Liver and gallbladder (155, 156)		12	1.6 (1.1–2.1)		
			Larynx (161)		14	1.2 (0.7–2.0)		
			Trachea, bronchus, and lung (160, 162)		137	1.5 (1.2–1.7)		
			Other respiratory (163–165)		15	4.2 (2.4–6.9)		
			Leukaemia (204–208)		12	0.8 (0.4–1.4)		
			Myeloma (203)		9	1.5 (0.7–2.8)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Lee *et al.* (2003) Cohort cancer incidence study Sweden	365424 male construction workers screened by the Organization for Working Environment, Occupational Safety and Health during 1971–93 and followed during 1971–99 through the Swedish National Cancer Registry	Wood dust exposure assessment based on a job–exposure matrix	Multiple myeloma (203)	Never exposed[1]	376	1.0 (reference)	RR[1] adjusted for BMI at entry to cohort	
				Ever exposed[1]	20	0.8 (0.49–1.20)		
				Never exposed[2]	376	1.0 (reference)	RR[2] adjusted for age, BMI, and other occupational co-exposures	
				Ever exposed[2]	20	0.8 (0.49–1.23)		
Jansson *et al.* (2005) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003) 260052 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Oesophogus (adenocarcinoma)	No exposure	61	1.0 (reference)	IRRs adusted for attained age, calendar year at entry into cohort, tobacco smoking at entry to cohort and BMI at entry to cohort	
				Moderate exposure	3	0.8 (0.2–2.5)		
				High exposure	0	0		
			Gastric (cardia; adenocarcinoma)	No exposure	152	1.0 (reference)		
				Moderate exposure	11	1.1 (0.6–2.0)		
				High exposure	2	4.8 (1.2–19.4)		
			Oesophagus (squamous cell carcinoma)	No exposure	170	1.0 (reference		
				Moderate exposure	8	0.7 (0.4–1.5)		
				High exposure	1	2.2 (0.3–15.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Purdue *et al.* (2006) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 307779 workers in cohort after excluding those missing smoking	Wood dust exposure assessment based on a job–exposure matrix	All sites (140–208)	Never exposed	490	1.0	RRs adjusted for age, smoking status and snuff use	
				Ever exposed	20	0.7 (0.4–1.0)		
			Oral cavity (140–145)	Never exposed	166	1.0		
				Ever exposed	5	0.5 (0.2–1.2)		
			Pharynx (146–149)	Never exposed	108	1.0		
				Ever exposed	4	0.6 (0.2–1.6)		
			Larynx (161)	Never exposed	216	1.0		
				Ever exposed	11	0.8 (0.5–1.5)		
Sjödahl *et al.* (2007) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 256357 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Gastric (non-cardia) (151)	Wood dust			RRs adjusted for age, smoking status and BMI	
				No exposure	892	1.0 (reference)		
				Moderate exposure	53	0.9 (0.7–1.2)		
				High exposure	3	1.2 (0.4–3.6)		

BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; RR, relative risk; SIR, standardized incidence ratio; standardized mortality ratio; yr, year or years

Table 2.3 Descriptive and linkage studies with results on exposure to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Pukkala et al. (2009) Census cancer incidence linkage Nordic countries	All incident cancer cases diagnosed in Denmark (1961–2005), Finland (1961–2005), Norway (1961–2005), Sweden (1961–2005) and Iceland (1961–2005)	Woodworkers includes workers who prepare and treat wood and make, assemble and repair constructions and products of wood	All cancers (140–208)	Men	74353	0.95 (0.95–0.96)	SIRs adjusted for age and calendar period	National rates use to calculate expected cancers
				Women	3004	0.92 (0.89–0.95)		
			Pharynx (146–149)	Men	450	0.83 (0.76–0.11)		
				Women	8	0.94 (0.4–1.9)		
			Nose (160)	Men	355	1.8 (1.7–2.04)		
				Women	10	1.9 (0.9–3.5)		
			Adenocarcinoma	Men	122	5.5 (4.6–6.6)-		
				Women				
			Larynx (161)	Men	819	0.82 (0.77–0.8)		
				Women	7	1.7 (0.5–3.9)		
			Lung (162)	Men	10941	0.96 (0.94–0.97)		
				Women	235	1.2 (1.1–1.4)		
			Mesothelioma (158, 162.2)	Men	494	1.6 (1.4–1.7)		
				Women	11	2.1 (1.1–3.8)		
			Stomach (151)	Men	4904	1.04 (1.01–1.07)		
				Women	133	1.1 (0.93–1.3)		
			Colon (153)	Men	5478	0.9 (0.88–0.93)		
				Women	206	0.88 (0.77–1.01)		
			Rectum (154)	Men	3988	0.97 (0.94–1.0)		
				Women	123	0.96 (0.8–1.14)		
			Hodgkin disease (201)	Men	382	1.04 (0.94–1.15)		
				Women	5	0.47 (0.15–1.11)		
			Non-Hodgkin lymphoma (200, 202)	Men	2170	0.97 (0.933–1.02)		
				Women	110	1.03 (0.85–1.24)		
			Multiple myeloma (203)	Men	1263	1.01 (0.96–1.07)		
				Women	47	1.03 (0.76–1.37)		
			Leukaemia (204)	Men	1898	0.96 (0.92–1.01)		
				Women	61	0.93 (0.71–1.19)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Weiderpass et al. (2001) Census linkage study Finland	2833 cases of endometrial cancers and 1101 cervical cancers diagnosed since 1971 in a cohort of 413877 skilled and specialized workers in Finland excluding farming occupations	Occupations were coded into job titles and a national job–exposure matrix (FINJEM) converted each job title into a probability and mean level of exposure	Endometrium	Wood surface finisher	8	1.8 (0.8–3.5)	SIRs adjusted for birth cohort, follow-up period, and social class	
				Low wood dust exposure	368	1.0 (0.9–1.2)		
			Cervix	High wood dust exposure	70	1.1 (0.8–1.4)		
				Woodworker, NEC	7	2.5 (1.0–5.1)		
				Plywood and fibreboard worker	24	1.6 (1.0–2.3)		
				Low wood dust exposure	249	1.2 (1.0–1.4)		
				High wood dust exposure	34	1.2 (0.9–1.7)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Arias Bahia *et al.* (2005) Registry-based study Brazil	138 male cases in wood-related jobs based on hospital records, 1991–99, 20+ yr of age Expected numbers based on male incident rates from the Belem population-based cancer registry. 2420 deaths among woodworkers compared to other deaths in the State of Para	Employment as a wood worker	Oral cavity and pharynx		8	1.7 (1.0–2.6)	Age	PCIRs – proportional cancer incidence ratios Belem (1988–89)
			Stomach		32	1.0 (0.7–1.5)		
			Colon		1	0.3 (0.0–1.7)		
			Rectum		3	1.1 (0.2–3.7)		
			Nasal cavity		1	1.5 (0.0–8.5)		
			Larynx		7	1.2 (0.5–2.4)		
			Lung		18	1.2 (0.7–1.9)		
			Hodgkin disease		3	2.2 (0.4–6.3)		
			Other lymphomas		0	0.0		
			Multiple myeloma		2	2.4 (0.3–8.8)		
			Leukaemia		4	1.4 (0.4–3.5)		
			Oral cavity and pharynx		18	1.0 (0.6–1.7)		CMORs – cancer mortality odds ratios State of Para (1980–95)
			Stomach		82	0.8 (0.7–1.1)		
			Colon		5	0.5 (0.2–1.2)		
			Rectum		8	1.3 (0.6–2.8)		
			Larynx		18	1.3 (0.6–2.8)		
			Lung		53	0.8 (0.6–1.0)		
			Hodgkin disease		5	1.1 (0.4–2.8)		
			Other lymphomas		11	1.4 (0.7–2.6)		
			Multiple myeloma		1	0.5 (0.0–3.4)		
			Leukaemia		7	0.6 (0.2–1.2)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Laaksonen et al. (2006) Census linkage study Finland	Incident cancer cases in all economically active Finns born during 1906–45 who participated in the national population census on 31 December 1970 (667121 men; 513110 women)	Exposure to wood dust: None (0) Low (< 3 mg/m³–yr) Med (3–50 mg/m³–yr) High (> 50 mg/m³–yr)	Nasal cavity (160)	None men	259	1.0 (0.9–1.1)	SIRs adjusted for age and social class	Exposure lag period 20 yr
				women	118	1.0 (0.8–1.2)		
				Low men	15	1.6 (0.9–2.6)		
				women	1	1.7 (0.0–9.7)		
				Med men	17	1.3 (0.8–2.1)		
				women	1	0.8 (0.0–4.4)		
				High men	1	1.2 (0.0–6.9)		
				women	0	0.0		
			Larynx (161)	None men	1965	1.0 (1.0–1.1)		
				women	128	1.0 (0.8–1.2)		
				Low men	76	1.1 (0.8–1.3)		
				women	1	1.2 (0.0–6.8)		
				Med men	77	0.7 (0.6–0.9)		
				women	3	2.1 (0.4–6.1)		
				High men	1	0.1 (0.0–0.7)		
				women	0	0.0		
			Lung (162)	None men	27309	1.0 (1.0–1.0)		
				women	3446	1.0 (1.0–1.0)		
				Low men	936	1.1 (1.0–1.2)		
				women	21	0.9 (0.6–1.4)		
				Med men	1784	1.0 (1.0–1.1)		
				women	48	1.0 (0.8–1.4)		
				High men	108	0.9 (0.7–1.0)		
				women	12	1.0 (0.5–1.7)		

CI, confidence interval; CMORs, cancer mortality odds ratios; PCIRs, proportional cancer incidence ratios; RR, relative risk; SIR,standardized incidence ratio; yr, year or years

2.2 Cancer of the nasopharynx

The previous *IARC Monograph* reviewed nine community-based case–control studies of cancer of the nasopharynx (see Table 25, IARC, 1995). The majority indicated an excess risk associated with either wood dust exposure (4/5 studies) or wood-related occupations (3/4 studies). Many of these studies had positive results based on very small numbers, and did not control for confounding. The studies were conducted in many different countries and odds ratios were generally in the range of 1.5–2.5. Among the studies that adjusted for the effects of smoking and alcohol, Vaughan (1989) and Vaughan & Davis (1991) observed an excess risk among carpenters (OR, 4.5; 95%CI: 1.1–19), and all woodworkers employed for 10 years or longer (OR, 4.2; 95%CI: 0.4–27). Sriamporn *et al.* (1992) observed an excess risk among wood cutters (OR, 4.1; 95%CI: 0.8–22).

None of the cohort studies reviewed by the previous *IARC Monograph* provided results for cancer of the nasopharynx, a rare tumour with an incidence rate of approximately 1/100000 in European countries.

In the period following the previous *IARC Monograph* (IARC, 1995), five new or updated cohort studies (Table 2.2) were published including a pooled re-analysis of five previously published cohort studies. Demers *et al.* (1995b) found an excess risk of cancer of the nasopharynx among workers classified as definitely exposed to wood dust (SMR, 5.3; 95%CI: 1.7–12.4, $n = 5$) and, overall, excesses were observed among both furniture (SMR, 2.4; 95%CI: 1.2–5.9, $n = 7$) and plywood workers (SMR, 4.6; 95%CI: 0.6–16.4, $n = 2$). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. The remaining cohort studies did not present results for this organ site.

Three new case–control studies (Table 2.5) have published results relevant for the evaluation of cancer of the nasopharynx. Armstrong *et al.* (2000) observed an increased risk associated with wood dust among Malaysian Chinese workers (OR, 2.4; 95%CI: 1.3–4.2). Vaughan *et al.* (2000) in a population-based study observed no increased risk overall (OR, 1.2; 95%CI: 0.5–2.7), and no evidence of an exposure–response relationship in analyses by maximum or cumulative exposure in a multicentre study in the USA. In another population-based study Hildesheim *et al.* (2001) found an increased risk overall (OR, 1.7; 95%CI: 1.0–3.0), which increased with both duration and cumulative exposure in Taiwan, China. It was also reported that these results were not affected by further adjustment for formaldehyde. One further hospital-based study reported an excess for nasopharyngeal and sinonasal cancer combined (Jayaprakash *et al.*, 2008).

2.3 Cancer of the pharynx

The previous *IARC Monograph* reviewed four case–control studies of cancer of the pharynx other than the nasopharynx (see Table 26, IARC, 1995). Two indicated an excess risk associated with wood-related occupations, although one was based on very small numbers. Another found mixed evidence. None of the cohort studies reviewed by that Working Group provided relevant results.

Four new case–control studies (Table 2.5) published since the previous *IARC Monograph* have results relevant for the evaluation of cancer of the pharynx other than the nasopharynx. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the hypopharynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–1.0). Laforest *et al.* (2000) observed no increased risk overall (OR, 0.9; 95%CI: 0.5–1.7), and only a slightly increased risk in the highest categories of cumulative exposure (OR, 1.5; 95%CI: 0.6–3.9). Berrino *et al.* (2003) found an increased risk of

Table 2.4 Case–control studies of sinonasal cancer and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Teschke *et al.* (1997) Population-based case–control study Canada	Nasal cavity and paranasal sinus (160)	All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr; 1990–92	Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex	Occupational histories obtained by interview and occupational exposures assessed by job classification	Hardwood dust Softwood dust	0.6 (0.1–3.0) 0.7 (0.3–1.6)	Sex, age (< 60, 60–69, ≥ 70), cigarette smoking (0–19, ≥ 20 pack–years)	
't Mannetje *et al.* (1999) Pooled population-based case–control study Italy, France, Netherlands, Germany, Sweden	Nasal cavity and paranasal sinus (160)	555 cases (104 women, 451 men) from 4 studies in Italy and 1 each from the Netherlands, France, Germany, and Sweden	1705 controls (241 women, 1464 men) from the same studies	Occupational history and job–exposure matrices were applied for wood dust	Wood dust exposure: Women Men Adenocarcinoma Squamous cell carcinoma	 1.2 (0.3–4.5) 2.4 (1.8–3.2) 12.2 (7.4–20.0) 0.7 (0.5–1.1)	Age group and study centre. Sex and smoking where applicable	
Pesch *et al.* (2008) Industry-based case–control study Germany	Nasal cavity and paranasal sinus (160)	86 male cases of adenocarcinoma of the nasal cavity and paranasal sinuses identified among workers with a recognized occupational disease during 1994–2003	204 controls randomly recruited from recognized accidents and falls frequency-matched to controls for age with 60 yr cut-off. Controls were also employed in the woodworking industries	Cumulative and average wood dust exposure quantified with a job–exposure matrix based on wood dust measurements at recent and historical workplaces	High exposure to: Hardwood Softwood Particle board Medium-density fibreboard	 4.0 (1.9–8.3) 0.3 (0.2–0.7) 0.5 (0.3–1.0) 0.3 (0.1–1.1)	Smoking, age, region, ever exposed to varnishes or stains	Only cases with successful compensation claims were used

Table 2.5 Case–control studies of cancer of the pharynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Gustavsson *et al.* (1998) Population-based case–control study Sweden	Pharynx (140–149)	401 incident squamous cell carcinomas, men aged 40–79 yr living in Stockholm or Southern health care region, 1988–91	Randomly selected from the base population, frequency-matched on region and age group	Occupational history, exposure assessment based on literature survey of exposure	Ever exposed	0.5 (0.3–1.0)	Region, age, alcohol consumption, smoking habits	
Armstrong *et al.* (2000) Population-based case–control study Malaysia	Nasopharynx (147)	282 Chinese cases identified between July 1990 and June 1992 through diagnosis records and/or treatment at centres with radiotherapy in the study area of Selangor & the Federal Territory	Matched by age (± 3yr) to 1 control in good health with no history of cancer of the head, neck or respiratory system, selected from Chinese population	Occupational histories were obtained by interview, exposure based on job	Any history of occupational exposure to wood dust	2.4 (1.3–4.2)	Diet and cigarette smoke indices, and matched on age	
Vaughan *et al.* (2000) Multicentred population-based case–control study USA 1987–93	Nasopharynx (147)	196 newly diagnosed cases in men & women, age 18–74 yr, from 5 registries (Connecticut, Detroit, Iowa, Utah and western Washington)	244 controls from the general population through random-digit dialling and frequency-matched to the cases by age (± 5yr), sex and cancer registry	Lifetime histories of occupational and chemical exposures taken by interview; estimates of exposures assessed on a job-by-job basis	Ever exposed Max exposure (mg/m^3): > 0.0–0.55 > 0.55–1.50 > 1.50 Cumulative (mg/m^3–yr): > 0.0–2.75 > 2.75–15.70 > 15.70	1.2 (0.5–2.7) 1.3 (0.5–3.6) 2.0 (0.5–8.1) 0.2 (0.0–2.1) 0.7 (0.2–2.5) 3.0 (0.9–9.8) 0.4 (0.1–2.3)	Age, sex, race, SEER site, cigarette use, proxy status, education and cumulative exposure to formaldehyde	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Laforest *et al.* (2000) Hospital-based case–control study France 1989–91	Hypopharynx (148)	296 men, incident squamous cell carcinomas, histologically confirmed from 15 hospitals	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, frequency-matched on age, same hospital or similar hospitals nearby, 1987–91	Detailed lifetime occupational history taken, occupational exposures were assessed through a job–exposure matrix	Ever exposed Probability: ≤ 70% > 70% Duration: < 6 yr 6–10 yr > 10 yr Cumulative: Low (< 10) Medium (10–42) High (> 42)	0.9 (0.2–4.1) 0.7 (0.3–1.8) 1.1 (0.5–2.3) 0.5 (0.2–1.5) 1.0 (0.3–2.9) 1.2 (0.5–3.0) 0.6 (0.2–1.6) 0.7 (0.3–2.3) 1.5 (0.6–3.9)	Age, smoking, alcohol, exposure to formaldehyde (yes/no), and mineral fibres (yes/no)	
Hildesheim *et al.* (2001) Population-based case–control study Taiwan, China July 1991 to December 1994	Nasopharynx (147)	375 newly diagnosed, histologically confirmed cases identified through two tertiary care hospitals in Taipei, Taiwan, China; < 75 yr of age, residents of Taipei city for 6+ mo	325 community controls matched to cases on sex, age and geographic residence by use of listings available through the National Household Registration System	Occupational history via interview, blindly assessed by an industrial hygienist for intensity and probability of exposure	Ever exposed Duration: ≤ 10 yr > 10 yr Cumulative: < 25 ≥ 25	1.7 (1.0–3.0) 1.2 (0.6–2.5) 2.4 (1.1–5.0) 1.2 (0.6–2.5) 2.4 (1.2–5.1)	Age, sex, education, ethnicity, and HLA	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Hypopharynx (148)	304 male incident cases from Calvados, France; Turin and Varese, Italy; Pamplona and Zaragoza, Spain; and Geneva, Switzerland	2176 male population controls	Occupational history through specialist interview; exposures assessed using a job–exposure matrix	< 55 yr of age: Possible exposure Probable exposure > 55 yr of age: Wood dust exposure	 0.3 (0.1–1.0) 0.4 (0.2–1.2) 2.1 (1.2–3.7)	Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
Vlajinac *et al.* (2006) Hospital-based case–control study Serbia & Montenegro 1998–2000	Oropharynx (146)	100 consecutive incident cases at the Clinical Centre of Serbia	100 controls among patients treated during the same period for non-malignant diseases of the head/neck, matched on age (± 2 yr), sex and place of residence	Occupational exposure to various chemicals, dust and other agents	Exposure to wood dust[1] Occupational exposure to wood dust[2]	2.3 (1.0–5.7) 4.2 (1.5–11.9)	[1]Education, BMI, smoking, alcohol, family history of cancers [2]Smoking, dental diseases, HSV infection, smoking, alcohol	
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Sinonasal & nasopharynx & hypopharynx (160, 147, 148)	90 incident cases in men diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure High exposure Occasionally exposed Regularly exposed	1.5 (0.9–1.5) 1.35 (0.4–4.6) 1.45 (0.85–2.5) 1.6 (0.75–3.3)	Age, sex, tobacco, education, year of enrollment	

BMI, body mass index; CI, confidence interval; HLA, human leukocyte antigen; HSV, herpes simplex virus; mo, month or months; yr, year or years

cancer of the hypopharynx among men over the age of 55 years (OR, 2.1; 95%CI: 1.2–3.7), and a decreased risk among men under 55 years (OR, 0.4; 95%CI: 0.2–1.2). Vlajinac *et al.* (2006) observed an increased risk of cancer of the oropharynx (OR, 2.3; 95%CI: 1.0–5.7) associated with wood dust in Serbia and Montenegro.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the pharynx, although none provided results for subsites of other than the nasopharynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the pharynx than expected (SMR, 0.8; 95%CI: 0.5–1.3). Stellman *et al.* (1998) also found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II (RR, 0.9; 95%CI: 0.4–2.0). Innos *et al.* (2000) found an excess risk of cancer of the pharynx among Estonian furniture workers exposed to both medium levels (SIR, 4.0; 95%CI: 0.8–11.8) and high levels of exposure (SIR, 1.5; 95%CI: 0.6–3.3). Dement *et al.* (2003) observed slightly more cases of cancer of the pharynx than expected among members of the US carpenters union (SMR, 1.4; 95%CI: 0.7–2.4). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.6; 95%CI: 0.2–1.6, $n = 4$).

2.4 Cancer of the larynx

The previous *IARC Monograph* reviewed ten case–control studies of cancer of the larynx (see Table 27, IARC, 1995). The majority had some indication of an excess risk associated with either wood dust exposure (1/2 studies) or wood-related occupations (7/8 studies), although sometimes based on small numbers. The studies were conducted in the USA ($n = 7$), Europe ($n = 2$), and the People's Republic of China ($n = 1$), and the majority of these studies adjusted for the effects of smoking. No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The five cohort studies that reported results for cancer of the larynx observed fewer cancers than expected.

Seven new case–control studies (Table 2.6) have published results relevant for the evaluation of cancer of the larynx. Pollán & López-Abente (1995) in a Spanish study observed an excess risk among woodworkers (OR, 2.7; 95%CI: 0.9–7.7) that increased with duration of employment. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the larynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–0.9). Laforest *et al.* (2000) observed no increased risk overall and no evidence of an association with duration or cumulative exposure in a french study (OR, 1.0; 95%CI: 0.6–1.7). Elci *et al.* (2002) also found no association with wood dust in a Turkish study (OR, 1.1; 95%CI: 0.8–1.4). Berrino *et al.* (2003) found an increased risk of cancer of the larynx among men over the age of 55 (OR, 1.7; 95%CI: 1.2–2.6), and a decreased risk among men under 55 (OR, 0.6; 95%CI: 0.3–1.1). Ramroth *et al.* (2008) reported an excess based on a checklist (OR, 2.1; 95%CI: 1.2–3.9), but a weaker association based on a method using a job-specific questionnaire (OR, 1.4; 95%CI: 0.8–2.5). Jayaprakash *et al.* (2008) reported an excess among men based on self-reported exposure (OR, 2.1; 95%CI: 0.9–5.0). Six of the seven studies adjusted for the potential effects of smoking and alcohol consumption, but the last only adjusted for smoking.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the larynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the larynx than expected (SMR, 0.7; 95%CI: 0.4–1.0), and no association with probability of exposure. Stellman *et al.* (1998) observed a potential excess risk associated with self-reported wood

Table 2.6 Case–control studies of cancer of the larynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Pallán & Lorez-Abente (1995) Hospital-based case–control study Spain January 1982 to August 1985	Larynx (161)	50 male residents of Madrid with histologically confirmed squamous cell carcinomas diagnosed at Ramon y Cajal Hospital	1 hospital control (matched by sex, age, admission date excluding alcohol or tobacco-related conditions) and 1 population control (matched on sex, age, residential census sections at diagnosis)	Extensive job history up to 1 yr before diagnosis; subject was considered exposed at ≥ 1 yr of employment	All woodworkers 1–20 yr > 20 yr	2.7 (0.9–7.7) 1.6 (0.4–5.9) 5.6 (1.2–27.6)	Age, tobacco and alcohol consumption, and other occupational groups	
Gustavsson *et al.* (1998) Community-based case–control study Sweden 1 January 1988 to 31 January 1991	Larynx (161)	401 incident squamous cell carcinomas in all Swedish men aged 40–79 yr living in Stockholm or the southern health care region	Referents randomly selected from the base population and frequency-matched to the cases for region and age group (40–54, 55–64, 65–79 yr)	Exhaustive occupational history taken and exposure assessments were based on a literature survey of exposure data for different occupations	Ever exposed	0.5 (0.3–0.9)	Adjusted for region, age, alcohol consumption and smoking habits	

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Lafores et al. (2000) Hospital-based case–control study France 1 January 1989 to 30 April 1991;	Larynx (161)	296 primary incident squamous cell cancers diagnosed and histologically confirmed in 15 French hospitals; only men were included in the study	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, selected by frequency matching on age and recruited between 1987 and 1991 in the same hospitals as the cases or similar hospitals nearby	Detailed lifetime occupational history taken and occupational exposures were assessed through a job–exposure matrix	**Wood dust** Ever exposed Probability of exposure: ≤ 70% > 70% Duration of exposure: < 6 yr 6–10 yr > 10 yr Cumulative level: Low (< 10) Medium (10–42) High (> 42)	1.0 (0.6–1.7) 0.9 (0.4–2.0) 1.1 (0.5–2.2) 1.4 (0.6–3.2) 0.5 (0.2–1.5) 1.0 (0.5–2.3) 1.0 (0.4–2.1) 1.2 (0.5–2.8) 0.9 (0.3–2.3)	Age, smoking, alcohol, exposure to formaldehyde, and mineral fibres	
Elci et al. (2002) Hospital-based case–control study Turkey 1979–84	Larynx (161)	940 cases among men identified from patients admitted to the Oncology Treatment Center of the Social Security Agency Okmeydani Hospital in Instanbul	1519 referent patients with Hodgkin disease, soft tissue sarcoma, non-melanoma skin cancer, testis, bone and male breast cancer as well as a series of non-cancer subjects	Occupational history taken using a questionnaire, occupations coded and exposures assessed using a job–exposure matrix developed for occupational dusts	Wood dust exposure Low intensity Med intensity High intensity Low probability Med probability High probability	1.1 (0.8–1.4) 0.8 (0.5–1.4) 1.4 (1.0–1.9) 0.8 (0.4–1.4) 1.3 (1.0–1.7) 1.4 (0.7–2.5) 0.4 (0.2–0.9)	Age, smoking, and alcohol consumption	

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Endolarynx (161)	696 male incident endolarynx cases diagnosed in Calvados, France; Turin & Varese, Italy; Pamplona & Zaragoza, Spain; Geneva, Switzerland	2176 male population controls	Occupational history taken through specialist interview; occupational exposures assessed using a job–exposure matrix	< 55 yr of age: Possible exposure Probably exposure > 55 yr of age Wood dust exposure	 0.5 (0.2–1.1) 0.6 (0.3–1.1) 1.7 (1.2–2.6)	Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Larynx (161)	124 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure High exposure Occasionally exposed Regularly exposed	0.8 (0.5–1.3) 2.1 (0.9–4.96) 0.8 (0.4–1.4) 1.5 (0.8–2.8)	Age, sex, tobacco, education, year of enrollment	
Ramroth *et al.* (2008) Population-based case–control study South-western Germany 1998–2000	Larynx (161)	257 histologically confirmed incident larynx cancer cases in men and women diagnosed in Rhein-Neckar-Odenwald region	769 population controls	Occupational history taken through specialist interview; occupational exposures assessed using exposure substance check-list (SCL), detailed occupational history, supplementary job-specific questionnaires (JSQ)	SCL: Wood dust Hardwood dust Softwood dust JSQ: Wood dust Hardwood dust Softwood dust	 2.1 (1.2–3.9) 2.6 (1.3–5.2) 2.2 (1.1–4.2) 1.4 (0.8–2.5) 1.2 (0.6–2.5) 1.5 (0.7–2.8)	Adjusted for age, sex, tobacco, alcohol, education	

CI, confidence interval; RR, relative risk; yr, year or years

dust exposure (RR, 1.6; 95%CI: 0.8–3.4, *n* = 8), but not for wood occupations (RR, 1.2; 95%CI: 0.3–4.9, *n* = 2) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed fewer cases of cancer of the larynx than expected (SIR, 0.7; 95%CI: 0.3–1.4) among male Estonian furniture workers. Dement *et al.* (2003) observed slightly more cases of cancer of the larynx than expected among members of the US carpenters union (SMR, 1.2; 95%CI: 0.7–2.0). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.8; 95%CI: 0.5–1.5).

Recent registry-based studies also presented results for wood dust and cancer of the larynx. No excess was observed among woodworkers in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias Bahia *et al.* (2005) observed a slight excess of cancer of the larynx in a Brazilian cancer registry and mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

2.5 Cancer of the lung

The Working Group for the previous *IARC Monograph* reviewed 24 case–control studies of cancer of the lung (see Table 28, IARC, 1995). Roughly half had some indication of an excess risk associated with either wood dust exposure or wood-related occupations. The studies were conducted in North America (*n* = 11), Europe (*n* = 9), Asia (*n* = 3), and New Zealand (*n* = 1). No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The seven cohort studies that reported results for cancer of the lung observed a similar number of cancers to that expected.

Three new case–control studies (Table 2.7) have published results relevant for the evaluation of cancer of the lung. Wu *et al.* (1995) observed an increased risk of non-small cell lung cancers among African- and Mexican-American men. Matos *et al.* (2000) observed an increased risk for lung cancer among sawmill workers, but not other woodworkers in Argentina. Barcenas *et al.* (2005) observed an excess of lung cancer associated with wood-related occupations or self-reported exposure in an American case–control study. All results were adjusted for smoking.

Four of the five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the lung. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the lung than expected (SMR, 0.8; 95%CI: 0.7–0.9). Stellman *et al.* (1998) observed a slight excess risk associated with self-reported wood dust exposure (RR, 1.2; 95%CI: 1.0–1.3), but not for wood occupations (RR, 1.1; 95%CI: 0.9–1.4) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed an increased risk among highly exposed female (SIR, 1.6; 95%CI: 0.8–2.9), but not among male Estonian furniture workers (SIR, 1.0; 95%CI: 0.8–1.3). Dement *et al.* (2003) observed an excess among members of the US carpenters union (SMR, 1.5; 95%CI: 1.2–1.7). In a nested case–control study of Polish pulp and paper mill workers, Szadkowska-Stańczyk & Szymczak (2001) observed an excess of lung cancer associated with wood dust exposure (OR, 2.1; 95%CI: 0.9–4.9), but no evidence of an exposure–response relationship.

Recent registry studies also presented results for wood dust and lung cancer. A small excess was observed among women (SIR, 1.2; 95%CI: 1.1–1.4) but not among men (SIR, 0.96; 95%CI: 0.94–0.97) in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias-Bahia *et al.* (2005) observed mixed results in Brazil; a slight excess in the cancer registry study and a decreased risk in the mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

Table 2.7 Case–control studies of cancer of the lung and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Wu *et al.* (1995) Hospital-based case–control study USA	Lung (162)	113 African-American and 67 Mexican-American cases with newly diagnosed lung cancer recruited from the hospitals in Houston and San Antonio, Texas	270 healthy controls without prior histories of cancer from community centres, cancer screening programmes, churches and employee groups frequency-matched on age, ethnicity and sex	Occupational histories collected by interview, self-reported occupational exposure to wood dust	Wood dust exposure African-American: Non-small cell lung cancer Small cell lung cancer Mexican-American: Non-small cell lung cancer Small cell lung cancer	3.5 (1.4–8.6) 4.8 (1.2–18.5) 0.7 (0.0–12.4) 3.8 (0.8–17.4) 0.3 (0.0–6.2)	Age, sex, mutagen sensitivity, and pack–yr (smoking)	.
Matos *et al.* (2000) Hospital-based case–control study Argentina 1994–96	Lung (162)	199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of 4 hospitals of Buenos Aires city	393 controls; 2 male control subjects hospitalized for conditions unrelated to tobacco use during the same period, and residents in the same area, matched by hospital and age (± 5yr)	Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix	Occupation in: Sawmills or wood mills Furniture Woodworkers (carpenters, cabinet-makers, machine operators)	 4.8 (1.2–19.0) 1.0 (0.4–2.2) 0.7 (0.3–1.5)	Age group, hospital, pack–yr and industries with $P < 0.05$	

Table 2.7 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Barcenas *et al.* (2005) Hospital-based case–control study USA July 1995 to October 2000	Lung (162)	1368 men and women with incident histologically confirmed lung cancer diagnosed at the University of Texas Cancer Center	1192 cancer-free enrollees of private multispecialty clinics; matched on gender and ethnic groups	Longest held occupation or industry, self-reported wood dust exposure obtained by interview; minimum of 1 yr	Wood related occupation/industry	3.2 (1.5–6.9)	Adjusted for age, gender, ethnicity, smoking status, and place of residence	
					Self-reported wood dust exposure	1.5 (1.2–2.1)		
					Occupation, industry, or self-reported exposure:			
					Lung (adenocarcinoma)	1.5 (1.0–2.1)		
					Non-small cell lung carcinoma (excluding adenocarcinoma)	1.9 (1.3–2.7)		
					Small cell lung carcinoma	1.1 (0.5–2.3)		
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Lung (162)	809 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure	1.1 (0.9–1.4)	Age, sex, tobacco, education, year of enrollment	
					High exposure	2.15 (1.3–3.6)		
					Occasionally exposed	1.1 (0.8–1.4)		
					Regularly exposed	1.7 (1.2–2.4)		

2.6 Other cancer sites

The results for other cancer sites were reviewed, but were less consistent than for the respiratory tract. The results for case–control studies for wood dust that were published subsequent to the previous *IARC Monograph* are presented in Table 2.8.

2.7 Furniture and cabinet-making industry

The Working Group also addressed the carcinogenic risk associated with the furniture and cabinet-making industry that was evaluated in the previous *IARC Monograph* Volume 25 (IARC, 1981), and reassessed in Supplement 7 (IARC, 1987) when it was classified as *carcinogenic to humans (Group 1)*. Since then, new studies and pooled analyses have strengthened the association between working in this industry and sinonasal and nasopharyngeal cancers, including Fukuda & Shibata (1988), Minder & Vader (1988), Magnani *et al.* (1993), Demers *et al.* (1995a, b) and Bouchardy *et al.* (2002). Such studies are listed among others published since 1980 in Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.9.pdf; Table to 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.10.pdf; Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.11.pdf; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.12.pdf; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.13.pdf; Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.14.pdf; Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.15.pdf; and Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.16.pdf.

From reviewing the studies in Tables 2.9 to 2.16 together with the data on exposure to wood dust in Tables 2.1 to 2.8, the Working Group attributed the causal association between working in the furniture and cabinet-making industry and sinonasal and nasopharyngeal cancers to wood dust.

Another possible association observed in the industry included excesses of pleural malignant mesothelioma, which is most likely the result of asbestos exposure. Another possible excess of haematopoietic malignancies may be the result to other exposures such as solvents. Relevant results are presented in Tables 2.11, 2.13 and 2.15 (online), but the Working Group considered data for these sites to be inconsistent and inadequate for evaluation.

2.8 Synthesis

There is consistent and strong evidence from both case–control studies and large cohort studies that wood dust causes sinonasal cancer. Most of these studies do not specify the histology of the tumours. Among the case–control that specified histology, very large excess risks were observed for sinonasal adenocarcinoma and wood dust exposure. Case series have found a large proportion of adenocarcinoma cases to be woodworkers.

There is also weaker evidence that wood dust causes cancer of the nasopharynx. The majority of case–control studies observed an increased risk of cancer of the nasopharynx associated with wood dust exposure or with employment in wood-related occupations, although often based on small numbers. This is supported by the pooled re-analysis of cohort studies where a strong association was observed with probability of wood dust exposure. The primary confounder of concern was formaldehyde exposure, but in the pooled cohort study the probability of wood dust exposure, which would likely be inversely correlated with formaldehyde exposure, was

Table 2.8 Case–control studies of other cancers and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Iriso[illegible] & Siemiatycki (1995) Population-based case–control study Canada 1979–85	Non-Hodgkin lymphoma (200, 202)	3730 male cases aged 35–70 yr, resident in Montreal, histologically confirmed non-Hodgkin lymphoma, Hodgkin disease, or myeloma	533 colorectal, bladder, prostate, stomach, kidney, melanoma, pancreas and oesophageal cancer controls. 533 population controls selected by electoral lists or random-digit dialling	Occupational history obtained by interview or questionnaire	Wood dust exposure: Non-substantial Substantial	 0.5 (0.3–0.8) 0.8 (0.5–1.3)	Age, proxy status, income (quintiles), ethnicity	Results for wood dust only presented for non-Hodgkin lymphoma
Cocco *et al.* (1998) Census-linked case–control study USA 1984–92	Gastric cardia (151.1)	1056 cases of gastric cardia cancer were identified in men aged 25 yr or more using death certificates from 24 states	5280 control subjects were identified the same way but who died of non-malignant disease; 5:1 match on region, sex, race, and age	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	Wood dust exposure: Unexposed All exposed Low level exposure Med level exposure High level exposure	 1.0 (reference) 0.8 (0.6–1.1) 0.9 (0.6–1.4) 0.7 (0.5–1.2) 1.0 (0.5–2.2)	Matched on region, sex, race, and age	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Cocco et al. (1999) Census-linked case–control study USA 1984–96	Stomach (151)	41957 deaths of stomach cancer aged 25+ yr using death certificates from 24 states	83914 controls who died of non-malignant disease; 2:1 match on region, sex, race, and age (± 5 yr)	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	White men: Med probability High probability Med intensity High intensity African-American men: Med probability High probability Med intensity High intensity White women: Med probability High probability Med intensity High intensity African-American women: Medium probability Medium intensity High intensity	0.9 (0.8–1.1) 1.0 (0.9–1.1) 1.0 (0.9–1.1) 0.9 (0.7–1.1) 1.0 (0.7–1.3) 0.9 (0.8–1.2) 1.1 (0.9–1.3) 0.8 (0.6–1.0) 0.7 (0.4–1.2) 0.8 (0.3–2.2) 0.9 (0.7–1.2) 0.7 (0.3–1.6) 1.3 (0.5–3.8) 0.9 (0.5–1.6) 0.4 (0.1–3.4)	Matched on region, sex, race, and age	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Mao et al. (2000) Registry-linked case–control study Canada 1994–97	Non-Hodgkin lymphoma (200, 202)	1469 histologically confirmed incident cases (764 men, 705 women) of non-Hodgkin lymphoma diagnosed in 8 Canadian provinces who were 20–74 yr of age	5073 controls frequency matched on age and sex randomly selected from within the same provinces via Provincial Health Insurance Plans, Property Assessment databases, or random-digit dialling	Home or work exposure to 17 chemicals was obtained through questionnaires or interviews	Wood dust exposure: Men Women Never exposed 1–6 yr exposure ≥ 7 yr exposure	0.9 (0.8–1.1) 1.4 (1.0–2.0) 1.0 (reference) 1.2 (0.7–1.9) 1.7 (1.1–2.6)	10-yr age groups, province, BMI (< 20, 20–27, > 27), consumption of milk	
De Roos et al. (2001) Population-based case–control study Canada & USA 1992–94	Neuroblastoma	538 incident cases under 19 yr of age at 139 participating hospitals	504 cases were identified through random-digit dialling individually caliper-matched to cases on date of birth	Telephone interviews with parents for maternal and paternal occupational history. Self-reported exposure assessed by an industrial hygienist (IH)	Wood dust exposure: Paternal occupational exposure Self-reported exposure IH-reviewed exposure	1.4 (0.8–2.3) 1.5 (0.8–2.8)	Child's age, maternal race, maternal age, and maternal education	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Briggs *et al.* (2003) Population-based case–control study USA 1984–88	Non-Hodgkin lymphoma (200, 202) Hodgkin disease (201)	1511 non-Hodgkin lymphoma, 343 Hodgkin disease cases diagnosed among African-American and white men born 1929–53, from Atlanta, Detroit, Connecticut, Iowa, Kansas, Miami, San Francisco, Seattle	1910 controls with no history of the selected cancer identified by random-digit dialling and frequency-matched by birth year, and geographic region of cancer registry	Occupational history collected by professional interviewers	Wood dust exposure: Non-Hodgkin lymphoma: African-American White Hodgkin disease: African-American White	 1.4 (0.7–2.8) 1.1 (0.9–1.3) 4.6 (1.6–13.3) 0.9 (0.7–1.3)	Age and cancer registry.	
Fritschi *et al.* (2005) Population-based case–control study Australia January 2000–August 2001	Non-Hodgkin lymphoma (200, 202)	Incident cases of non-Hodgkin lymphoma diagnosed in New South Wales or the Australian Capital Territory; aged 20–74 yr	Controls were randomly selected from the New South Wales and Australian Capital Territory Electoral Rolls, frequency matched on age, sex and region of residence	Lifetime occupational history obtained by telephone interview & mailed questionnaire. Exposure assessment done blindly by an occupational hygienist and a job–exposure matrix	Hardwood dust exposure: Non-substantial Substantial Softwood dust exposure: Non-substantial Substantial	1.5 (0.9–2.4) 1.7 (1.0–2.9) 1.2 (0.6–2.7) 1.6 (1.1–2.6) 1.7 (1.0–2.8) 1.6 (0.7–3.8)	Adjusted for age, sex, state and ethnic origin	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Pan *et al.* (2005) Registry-linked case–control study Canada 1994–97	Brain (191)	1009 incident cases of histologically confirmed primary brain cancer from 8 provinces	5039 population control subjects aged 20–76 yr collected in the same study area	Occupational history obtained through questionnaires. Self-reported exposure	Wood dust exposure: Men Women Both sexes	 1.3 (1.9–1.4) 1.1 (0.8–1.7) 1.2 (1.0–1.4)	Age, province of residence, education, alcohol intake, total energy intake, smoking pack–yr, and sex	
Fritschi *et al.* (2007) Population-based case–control study Australia January 2001–August 2002	Prostate (185)	606 histologically confirmed cases in Western Australia, aged 40–75 yr. 402 cases of benign prostatic hyperplasia identified from hospital records	471 controls aged 45–75 yr randomly selected from the Western Australia electoral roll August 2001–October 2002; frequency-matched on 5 yr age groups	Occupational history obtained by questionnaires and interviews. Exposure was assessed for each occupation by an occupational hygienist for probability, frequency and total dose.	Wood dust exposure: Prostatic cancer– Not exposed Non-substantial Substantial Benign prostatic hyperplasia– Not exposed Non-substantial Substantial	 1.0 (reference) 1.1 (0.8–1.4) 1.2 (0.5–2.6) 1.0 (reference) 1.1 (0.8–1.4) 0.8 (0.4–1.4)	Adjusted for age	

BMI, body mass index; yr, year or years

associated with nasopharyngeal cancer risk, and an excess was observed among both the furniture workers and plywood workers subcohorts.

There was weaker evidence for other sites such as the pharynx, larynx, and lung. Although positive associations were observed in some case–control studies, the pattern was not as consistent and not supported by positive findings in cohort studies.

The great majority of studies did not report on the specific tree species to which workers were exposed or whether exposure was due primarily to hardwoods or softwoods. The few studies that did address tree species were relevant only for the evaluation of sinonasal cancer. There is strong evidence for an association between sinonasal cancer and exposure to hardwood dusts, based on the results of the few studies that specifically assessed exposure to hardwoods and on the results of case series that identified specific tree species. Among the few case–control studies that assessed the relationship with softwoods, there was a consistent excess risk, but the magnitude of the excess was small in comparison to hardwoods, and the association was primarily with squamous cell carcinoma.

3. Cancer in Experimental Animals

Only a limited number of studies in experimental animals have been published on the carcinogenicity of wood dust. Studies described below include those summarized in the previous *IARC Monograph* (IARC, 1995) as well as studies published since.

3.1 Inhalation

3.1.1 Rat

An inhalation study to determine the carcinogenicity of inhaled oak wood dust with and without wood preservatives was conducted in rats. Six groups of 58–61 female F344 rats were exposed to: 1) 18 mg/m^3 of untreated oak wood dust; 2) wood preservatives containing 1 μg/m^3 lindane and 0.2 μg/m^3 pentachlorophenol (PCP); 3) oak wood dust treated with lindane and PCP; 4) 21 μg/m^3 of sodium dichromate; 5) oak wood dust treated with chromate (wood contained the equivalent of 39 μg/m^3 chromate); and, 6) 72 μg/m^3 of *N*-nitrosodimethylamine (positive control). A group of 115 rats were sham-exposed (negative control). Approximately 24 rats/group were exposed for 25 weeks and approximately 36 rats/group were exposed for their lifespan. The particle size was reported as 2–7 μm. The untreated wood dust contained up to 5 μg/m^3 of chromate. No respiratory tract tumours were observed in the negative controls. The positive control group of animals exposed for their lifespan had an incidence of 12/35 nasal cavity tumours. Respiratory tract tumours occurred less frequently in animals exposed for only 25 weeks than in those exposed for their lifespan. The only significant finding in rats exposed for 25 weeks was an increased incidence over controls of benign tumours of organs other than the respiratory tract in the group exposed to chromate aerosol alone. In the rats exposed to untreated oak wood for their lifespan, 2/36 rats developed malignant tumours of the respiratory tract (one in the oral cavity, one bronchial carcinoma, but none in the nasal cavity); there were no benign tumours of the respiratory tract. There was 1/37 animals exposed to wood dust treated with chromate stain, and 1/34 animals exposed to chromate aerosol for their lifespan that had a nasal cavity tumour, but none were found in the rats exposed to untreated wood dust (Klein *et al.*, 2001).

Sixteen female Sprague Dawley rats were exposed to 25 mg/m^3 of untreated beech wood dust (70%, ≤ 10 μm; 10–20%, ≤ 5 μm) for 6 hours/day, 5 days/week for 104 weeks. There were 16 untreated controls. In the 15 surviving exposed rats and 15 control rats, no respiratory tract

tumours were observed. Incidences of non-respiratory tract tumours did not differ between untreated and exposed rats (Holmström *et al.*, 1989).

Fifteen female Wistar rats were exposed to 15.3 mg/m^3 of beech wood dust (mass median aerodynamic diameter [MMAD], 7.2 µm; geometric standard deviation [GSD], 2.2) for 6 hours/day, 5 days/week, for 6 months, and were observed for up to 18 months. No respiratory tract tumours were found in exposed rats or in 15 untreated controls. The incidence of non-respiratory tract tumours did not differ between exposed rats and untreated controls (Tanaka *et al.*, 1991).

3.1.2 Hamster

One group of 12 and one group of 24 male Syrian golden hamsters were exposed to either 15 or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for either 36 or 40 weeks, respectively. One group of 12 and one group of 24 animals served as untreated controls. No respiratory tract tumours were observed in the 12 animals exposed to 15 mg/m^3, but 1/22 animals exposed to 30 mg/m^3 had an unclassifiable infiltrating malignant nasal tumour (not significantly different from controls) (Wilhelmsson *et al.*, 1985a, b). [The Working Group noted that in the above inhalation studies, the size of the dusts was quite large, which might allow some deposition in the upper respiratory tract, but very little deposition in the lower respiratory tract. No measurement of deposition was made, so the actual exposure is unknown.]

3.2 Intraperitoneal injection

3.2.1 Rat

Female Wistar rats received three weekly intraperitoneal injections of beech wood dust [total dose reported as 250 or 300 mg/animal] suspended in saline, and were held for 140 weeks. No mesotheliomas or sarcomas were reported in the 52 rats examined (Pott *et al.*, 1989). [The Working Group noted the limited reporting of the study. No details on the number of starting animals or on particle size were given.]

3.3 Administration with known carcinogens or other modifying factors

3.3.1 Rat

Four groups of 16 female Sprague-Dawley rats were exposed 6 hours/day, 5 days/week for 104 weeks by inhalation to: air (control); 25 mg/m^3 untreated beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm); 14.9 mg/m^3 formaldehyde; or wood dust plus formaldehyde. Metaplastic or dysplastic lesions were observed in rats exposed to formaldehyde with or without wood dust, but the incidences between both groups were not statistically different. No such lesions were observed in control rats or in rats exposed to wood dust alone. No respiratory tract tumours were observed in rats exposed to wood dust or to wood dust plus formaldehyde (Holmström *et al.*, 1989).

Two groups of 20 male Wistar rats were exposed by inhalation to air (control); or 15 mg/m^3 of beech wood dust (MMAD, 7.2 µm; GSD, 2.2) for 6 hours/day, 5 days/week for 6 months. Thereafter, five rats per groups were exposed to 10.2 mg/m^3 of sidestream cigarette smoke for 2 hours/day, 5 days/week for 1 month. The experiment was terminated 18 months after the start of the exposures. No tumours of the respiratory tract were observed (Tanaka *et al.*, 1991).

3.3.2 Hamster

Two groups of 12 male Syrian golden hamsters were exposed by inhalation to air (control) or 15 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 36 weeks. Another two groups of hamsters were treated similarly but also received weekly subcutaneous injections of 1.5 mg *N*-nitrosodiethylamine (NDEA) for the first 12 consecutive weeks. No nasal tumours were observed in the four groups. Tracheal squamous cell papilloma incidences were: 1/7, controls; 0/8, wood dust; 3/8, NDEA; 4/8, NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

Two groups of 24 male Syrian golden hamsters were exposed by inhalation to air or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 40 weeks. Another two groups of hamsters were treated similarly but received weekly subcutaneous injections of 3 mg NDEA for the first 12 consecutive weeks. No respiratory tract tumours were found in control animals. The incidence of these tumours did not differ between the groups treated with NDEA or NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

3.4 Exposure to wood dust extracts

In a lifetime experiment, four groups of 70 female NMRI mice weighing 25–30 g [age unspecified] received skin applications of a mutagenic fraction of a methanol extract of beech wood dust in 30 µL acetone twice a week for 3 months. Positive and negative controls were included in the study (Table 3.1). No effect on survival was observed between the treated groups and the negative control groups. A comparison between mice treated with wood dust extract and mice serving as negative controls indicated an overall carcinogenic effect ($P < 0.01$, χ^2 test) (Mohtashamipur *et al.*, 1989). [The Working Group also noted a dose-dependent increase in the incidence of skin squamous cell papillomas and carcinomas combined or papillomas alone.]

Four groups of 50 male and female Kunming mice were intragastrically administered 0, 1, 2 or 4 g/kg body weight of a water extract of birch wood dust, once a week for 5 weeks. Thereafter, mice were given 0.5% butylated hydroxytoluene for 3 weeks in the diet. The experiment was terminated at experimental Week 15. There was a dose-dependent increase ($P < 0.05$) in lung tumour incidence (0/50, 2/49, 4/48, 7/49, respectively), and multiplicity (0, 0.04, 0.15, 0.24 tumour/mouse, respectively). No significant increase was observed in a similar experiment using an organic extract of birch wood dust (He *et al.*, 2002).

3.5 Exposure to wood shavings

Studies directed at testing the potential carcinogenicity of cedar shavings were inadequate in that they did not have control groups (Vlahakis, 1977; Jacobs & Dieter, 1978).

3.6 Synthesis

Several of the studies investigating the carcinogenicity of inhaled wood dust in rats and hamsters used particles with relatively large MMADs, a design that would enhance deposition in the upper respiratory tract, including the nasal cavity. Despite this design, the results of the animal studies do not confirm the nasal carcinogenicity of wood dust observed in humans. No measurement of the actual deposition of wood dust in the respiratory tract was made, and therefore the amount of the exposure is unknown.

In one study in mice, a methanol extract of beech wood dust was tested by skin application. Although a dose-dependent increase in the incidence of skin tumours was observed, this result cannot be used in the evaluation of the carcinogenicity in experimental animals of wood dust per se.

Table 3.1 Study in mice exposed to mutagenic fractions of dust[a]

Tumour	Negative controls			Extract (g)				Benzo[*a*]pyrene (µg)	
	Untreated (n = 43)	Shaven (n = 44)	Shaven, acetone-treated (n = 42)	2.5 (n = 43)	5.0 (n = 50)	7.5 (n = 46)	10.0 (n = 49)	5 (n = 43)	10 (n = 42)
Skin squamous cell carcinomas	–	–	–	1	–	–	1[b]	1	15
Skin squamous cell papillomas	–	–	–	1	1	6	5[b]	2	5
Skin keratoacanthomas	–	–	–	–	–	1	–	–	2
Skin papillary cystadenomas	–	–	–	–	1	–	–	–	–
Sebaceous gland adenomas	–	–	–	–	–	–	–	2	–
Mammary gland adenocarcinomas	–	–	–	–	4	3	2	1	1
Mammary gland adenoacanthomas	–	–	–	–	–	–	1	–	–
Mammary gland mixed tumours	–	–	–	–	–	–	2	–	–
Fibrosarcomas	–	–	–	–	–	1	–	–	–
Haemangiosarcomas	–	–	–	–	1	–	–	–	–
Neurofibrosarcomas	–	–	–	–	1	–	–	–	–
Lymphomas	–	–	–	–	–	–	1	–	–
Anaplastic carcinomas	–	–	–	–	1	–	–	–	–
Precancerous skin lesions	–	1	2	2	4	8	6	13	18

[a] Dust from untreated, semidry beech wood

[b] [$P < 0.01$; Cochran-Armitage test for trend] where comparisons are made for 0 (acetone-treated controls), 2.5, 5.0, 7.5 and 10 g extract groups, including squamous cell carcinomas and papillomas combined, or papillomas alone

Adapted from Mohtashamipur *et al.* (1989), numbers of animals given are effective numbers

4. Other Relevant Data

4.1 Deposition and clearance of particulates in the nasal region

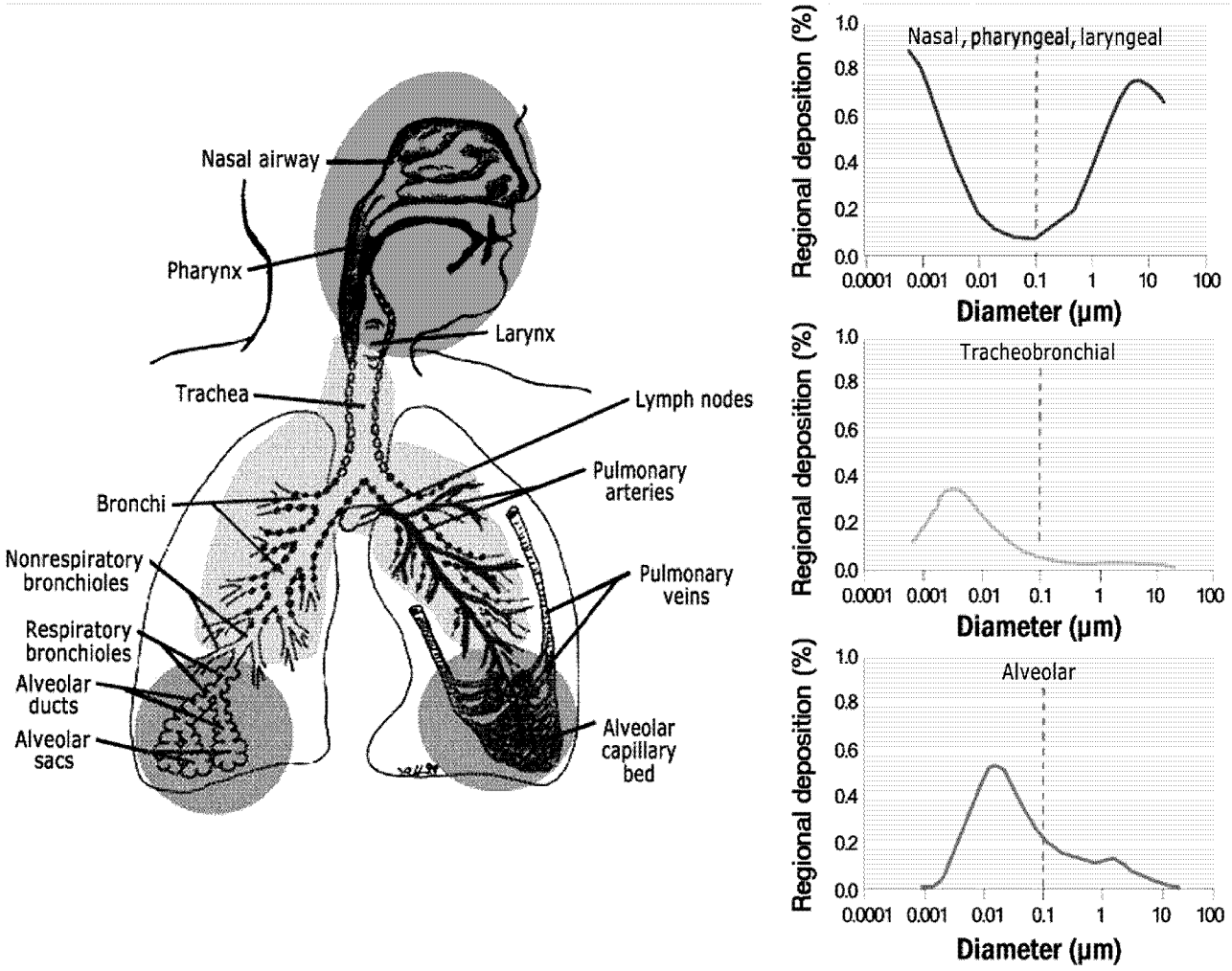
The anatomy and physiology of the upper respiratory tract is complex, and there are significant differences between rodents, non-human primates, and humans (reviewed by Stuart, 1984; Harkema, 1991). Wood dust, leather dust, and metal-containing dusts are complex mixtures that have been associated with the development of sinonasal and nasopharyngeal cancers in humans (IARC, 1995). The nasal region is a primary target of inhaled toxicants. In humans, the particulate fraction of wood and leather dusts is considered to be responsible for carcinogenesis (Fu *et al.*, 1996; Feron *et al.*, 2001). Particulate dosimetry in the upper respiratory tract depends on anatomy, airflow dynamics, and histology. Three-dimensional models have been developed to facilitate interspecies comparisons (Anjilvel & Asgharian, 1995). Humans vary in their breathing patterns at rest and at work; these patterns have an impact on the extent of nasal deposition of particles. In humans, coarse particles (2.5–10 μm) deposit by impaction in the nasal region; very fine particles (less then 0.01 μm in diameter) deposit in the nasopharynx by diffusion (Fig. 4.1; reviewed in Oberdörster *et al.*, 2005). Coarse particles deposited in the nose are rapidly removed by sneezing, sniffing, and mucociliary clearance. However, some areas in the nasopharynx lack cilia, and particles deposited in these regions have longer retention times that can be up to several days (Feron *et al.*, 2001).

4.2 Molecular pathogenesis

The histopathological classification of cancers arising in the sinonasal region (nasal cavity and paranasal sinuses) and in the nasopharynx varies with the anatomical location and associated risk factors (Rosai, 2004). In the sinonasal region, benign tumours or sinonasal papillomas occur; the inverted papilloma subtypes may progress to malignant squamous cell carcinomas in 3–13% of cases (Littman & Vaughan, 2006). The most common malignant tumour in the sinonasal region is squamous cell carcinoma, which is usually associated with cigarette smoking ('t Mannetje *et al.*, 1999), and rarely following exposure to wood dust (see Section 2). Adenocarcinomas are strongly associated with exposure to wood and leather dusts (Fu *et al.*, 1996; d'Errico *et al.*, 2009). Wood dust exposure was associated with a 21-fold [95%CI: 8.0–55.0] increase in the risk of having a sinonasal adenocarcinoma or a squamous cell carcinoma compared to not being exposed (Bornholdt *et al.*, 2008). These occupationally related carcinomas have a unique histological appearance described as intestinal-type sinonasal adenocarcinoma (ITAC). The majority of ITACs are localized in the superior nasal cavity and ethmoid sinus. This cancer develops after a long latent period of 20–30 years of exposure to wood dust, and is locally invasive with rare distant metastases (Llorente *et al.*, 2009). Other malignant sinonasal cancers include cylindrical (transitional) cell carcinoma, small cell neuroendocrine carcinoma, and undifferentiated (anaplastic) carcinoma (Rosai, 2004).

In the nasopharynx, the histopathological classification varies with age and associated risk factors (Yu & Yuan, 2006). Keratinizing squamous cell carcinomas occur at older ages, and the majority of nasopharyngeal carcinomas are non-keratinizing carcinomas, either differentiated or undifferentiated (Rosai, 2004). Non-keratinizing nasopharyngeal carcinomas are more common in high-risk populations in association with Epstein-Barr virus infection and other risk factors as discussed in Section 4.4.

Fig. 4.1 Deposition of inhaled particles in the human respiratory tract during nasal breathing



From Oberdörster *et al.* (2005). Drawing courtesy of J Harkema. Reproduced with permission from Environmental Health Perspectives.

4.2.1 Cancer of the nasal cavity and paranasal sinuses

These cancers are extremely rare with only an overall annual incidence of approximately 1/100000 in Europe (Muir *et al.*, 1987). There have been few studies of molecular and genetic alterations associated with the development of sinonasal cancers, and no link to chemical carcinogens has been established (Saber *et al.*, 1998). Inverted papilloma is recognized as a preneoplastic lesion, and mutations in the *p53* tumour-suppressor gene have been associated with progression to squamous cell carcinoma. Epigenetic alterations characterized by promoter hypermethylation have also been identified in sinonasal papilloma (Stephen *et al.*, 2007). In ITACs of patients with known long-term exposure to wood or leather dust, $p14^{ARF}$ and $p16^{INK4a}$ promoter methylation was detected in 80% and 67% of cases, respectively (Perrone *et al.*, 2003). In the same study, *p53* mutations were present in 44% (7/16 cases) of the ITACs, and in all but one case the mutations were G:C→A:T transitions in 86% of the cases, and involved the CpG dinucleotides in 50% of the cases. Loss of heterozygosity at chromosomal loci encoding the *p53* (locus 17p13), $p14^{ARF}$ and

p16^{INK4a} (locus 9p21) genes were also reported in 58% and 45% of the cases, respectively (Perrone *et al.*, 2003). *p53* Mutations were previously reported in only 18% (2/11) of sinonasal adenocarcinomas from patients with unknown exposure (Wu *et al.*, 1996). *K-RAS* mutations were also reported in ITACs with a frequency of 13%, whereas the frequency was very low (1%) in squamous cell carcinoma (Saber *et al.*, 1998; Bornholdt *et al.*, 2008). Strikingly, among the five mutations located in codon 12 of the *K-RAS* gene, the G→A transition was the most common, and was present in tumour tissue (adenocarcinoma) from two wood-dust-exposed patients and from one patient with unknown exposure (Bornholdt *et al.*, 2008). [The Working Group noted that a clear link between exposure to wood or leather dust and specific G:C→A:T transitions in ITACs remains to be demonstrated.] Although ITACs resemble colonic adenocarcinomas histologically, alterations in *E-cadherin* and *β-catenin* genes characteristic of the APC pathway and alterations in mismatch-repair genes are rare in sinonasal adenocarcinomas (Perez-Ordonez *et al.*, 2004).

Unique patterns of chromosomal gains and losses have been associated with wood-dust-related ITACs (Korinth *et al.*, 2005; Llorente *et al.*, 2009). Overexpression of c-erbB2 protein was found in one-third of cases (Gallo *et al.*, 1998).

There are no identified precursor lesions leading to the development of ITACs, although hyperplasia, squamous metaplasia, and dysplasia occur frequently in areas adjacent to sinonasal carcinomas (Llorente *et al.*, 2009). A morphological study of nasal biopsies from 139 leather workers employed for a median of 29 years revealed squamous metaplasia in 65% of cases, dysplasia in 41% of cases, and goblet cell hyperplasia in 22% of cases. The presence of goblet cell hyperplasia was associated with longer occupational exposures in leather-tanning activities (Palomba *et al.*, 2008).

4.2.2 Cancer of the nasopharynx

There are few studies of molecular alterations in cancer of the nasopharynx. Many genetic alterations (chromosomal gains and losses) have been described in endemic nasopharyngeal carcinomas, but none of these changes have been specifically linked to wood or leather dust exposure (Hui *et al.*, 1999; Chan *et al.*, 2002).

4.3 Mechanisms of toxicity and carcinogenicity

4.3.1 Tissue injury

Histopathological changes associated with tissue injury and repair (metaplasia, hyperplasia) are extremely common in the upper respiratory tract of experimental animals and humans. In rats, the inhalation of a wide range of volatile and semi-volatile industrial chemicals induces tissue injury, inflammation, and hyperplasia; however, there is no consistent association with subsequent development of nasal cancer. Inflammation, IgE-mediated allergic rhinitis associated with the inhalation of particulate antigens, and inflammatory sinonasal polyps are very common in humans, yet sinonasal cancers are rare as discussed in Section 4.2. Common histopathological changes found in the nasal epithelium include cuboidal and squamous metaplasia and hyperplasia of goblet cells and cylindrical cells. These reactive changes are not considered to be precursors for the development of neoplasia. It is possible that wood dust particles incite tissue injury by direct mechanical damage, although there are no experimental data to support this mechanism (Feron *et al.*, 2001).

4.3.2 Impaired ciliary clearance and mucostasis

Heavy occupational exposure to wood dust has been reported to impair ciliary clearance, and to contribute to mucostasis (IARC, 1995). Theoretically, the impaired clearance of wood dust particles could lead to prolonged contact with the upper respiratory epithelium (Littman & Vaughan, 2006). Impaired mucociliary clearance may also allow particulate antigens to gain entry to nasal-associated lymphoid tissues, and enhance allergic sensitization (Feron *et al.*, 2001).

4.3.3 Direct genotoxicity

Direct genotoxic effects of wood dust extracts were summarized in IARC (1995). Overall, the mutagenic activity of beech and oak wood extracts was detected in bacterial systems and in rat hepatocytes *in vitro*. Several chemicals were isolated from wood extracts, but only quercetin and Δ^3-carene were shown to be mutagenic (IARC, 1995). Exposure to hexavalent chromium has been associated with the development of sinonasal cancers (Sunderman, 2001).

Dust particles may act as carriers for genotoxic agents. Chromium compounds are often present in oak and beech dusts as they are frequently used in the wood-processing industry, particularly as potassium dichromate in stains as well as fixing agents in wood preservatives. Stained furniture is made largely from oak and beech as they contain enough tannic acid to allow for chemical staining (Klein *et al.*, 2001). Nasal tumours were produced in rats following the inhalation of chromate-stained oak wood dust Klein *et al.* (2001). It was hypothesized that chromate trapped in dust particles is slowly released as hexavalent chromium in the nasal mucosa. Leather workers and tanners are also exposed to hexavalent chromium (Stern *et al.*, 1987). Hexavalent chromium is genotoxic and has been linked with the development of sinonasal cancers in humans (Table 4.1; IARC, 1990).

Table 4.1 Other risk factors for cancers of the nasal cavity and paranasal sinuses[a]

Exposure	Reference
Boot and shoe manufacture and repair	IARC (1987, 2012b)
Formaldehyde	IARC (1995, 2012d)
Hexavalent chromium	IARC (1990, 2012b)
Mineral oils	IARC (1987, 2012d)
Mustard gas	IARC (1987, 2012d)
Selected nickel compounds	IARC (1990, 2012b)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens by IARC

DNA damage (detected by comet assay) in peripheral blood leukocytes was studied in 35 furniture workers and in 41 control office workers. Approximately 20% of woodworkers had elevated levels of DNA damage that did not depend on smoking status compared to 13% of control smokers and 7% of control non-smokers (Palus *et al.*, 1999). [The Working Group noted that the significance of this study is difficult to assess because DNA damage in the sinonasal mucosa was not studied.]

Another group of 60 male furniture workers occupationally exposed for more than 5 years to a mixture of softwood and hardwood dusts (7.4–25.8 mg/m^3) was studied for markers of genotoxicity using peripheral blood lymphocytes and buccal epithelial cells. Controls were 60 healthy male government workers with no history of wood dust exposure. Statistically significant elevations in DNA damage in peripheral blood lymphocytes were detected in workers using the Comet assay. Increased frequencies of micronuclei and chromosomal aberrations were also detected in the peripheral blood lymphocytes of workers. An increased frequency of micronuclei was also detected in buccal epithelial cells obtained from workers. Micronucleus frequency was increased in both workers and controls who were smokers and consumed alcohol. Serum

levels of superoxide dismutase activity and glutathione peroxidase activity, but not catalase activity, were reduced in the workers (Rekhadevi *et al.*, 2009). [The Working Group noted that the authors of this study could not eliminate a potential effect of exposure to chemical adhesives and wood polish in these workers.]

Çelik & Kanik (2006) studied the frequency of micronuclei and other nuclear alterations in exfoliated buccal mucosal cells from 20 workers occupationally exposed to wood dust and 20 healthy controls. Dust levels in the workplace were 4.7–28.9 mg/m^3. In the controls, the micronucleus frequency was 1.5 ± 1.2% compared to 6.6 ± 1.6% in the workers. Evidence of nuclear injury (karyolysis, karyorhexis) and binucleated cells was also increased in the workers. Smokers in both groups showed increased micronucleus frequency and evidence of nuclear injury. [The Working Group noted that the use of buccal epithelial cells as a surrogate for sinonasal mucosa had not been validated.]

The genotoxicity of six wood dusts and dust from MDF coated with oak was compared in the A549 human lung carcinoma cell line (Bornholdt *et al.*, 2007). As determined by a comet assay, beech, birch, teak, pine, and MDF dusts increased DNA strand breaks 1.2–1.6-fold after 3 hours of exposure. [The Working Group noted that the use of a malignant lung carcinoma cell line as a surrogate for sinonasal epithelial cells is questionable, and that no particulate control group was included.]

No data based on genotoxic assays were available to the Working Group for workers exposed to leather dusts.

4.3.4 Indirect genotoxicity

The most likely mechanism proposed for the carcinogenicity of wood dust is a combination of reduced clearance of large particles from the middle turbinate and ethmoid regions of the sinonasal cavity, leading to mechanical irritation, inflammation, and increased cell proliferation (Llorente *et al.*, 2009). In support of the association between chronic inflammation and sinonasal cancer, Holmila *et al.* (2008) analysed COX-2 and p53 protein expression in 23 cases of adenocarcinoma; 17 were exposed to wood dust and 19 were smokers. Elevated COX-2 expression was found in 13 cases including eight cases who were non-smokers; ten of these cases had a history of wood dust exposure. In 50% of the cases with elevated COX-2 expression, there was elevated p53 protein expression in the same histological pattern as COX-2. COX-2 protein expression was confirmed at the mRNA level.

In a murine model of lung inflammation induced by intranasal instillation of birch or oak dusts two times a week for 3 weeks, oak dust induced more inflammation with an influx of neutrophils and lymphocytes compared with birch dust that elicited an influx of eosinophils (Määttä *et al.*, 2006).

These dusts were also tested for induction of pro-inflammatory mediators from murine RAW 264.7 macrophage cell lines. Birch dust increased the release of the pro-inflammatory cytokines IL-6 and TNF-α, and oak dust caused a smaller release of TNF-α. Birch dust also elicited a stronger chemokine response than oak dust (Määttä *et al.*, 2005).

A panel of six wood dusts and MDF dust was assessed for expression of IL-6 and IL-8 pro-inflammatory cytokines using the human A549 lung carcinoma cell line. Based on expression of IL-8 mRNA, teak dust was more potent than MDF, birch, spruce, or pine dust; with beech and oak dust showing the weakest activity in this assay (Bornholdt *et al.*, 2007).

Human alveolar macrophages obtained from healthy volunteers were exposed to endotoxin-free pine dust for 2 hours. This exposure induced a dose-dependent release of the pro-inflammatory mediators, TNF-α and MIP-2, that was associated with increased production of reactive oxygen species (Long *et al.*, 2004).

No experimental data were available to the Working Group on the release of inflammatory mediators from animals or cell cultures following exposure to leather dusts.

Overall, these experimental studies provide evidence that wood dust from a variety of hardwoods and softwoods can elicit the release of pro-inflammatory mediators after short-term exposures, and suggest a possible association between inflammation and the development of cancer.

In summary, the mechanism responsible for the carcinogenicity of wood or leather dusts is unknown as concluded previously by IARC (1995). In 2000, the Health Council of the Netherlands concluded that wood dust cannot be classified as a non-genotoxic carcinogen or as a direct or indirect genotoxic carcinogen due to insufficient mechanistic data (Feron *et al.*, 2001).

4.4 Other risk factors for sinonasal and nasopharyngeal cancers

The most important exposures associated with the development of sinonasal cancers are occupational exposures in furniture and woodworking industries, leather and shoe manufacturing, and in nickel workers (Table 4.1; IARC, 2012b).

Exposures to other agents classifed by IARC as *carcinogenic to humans (Group 1)* have also been associated with cancers of the nasal cavity and paranasal sinuses (Table 4.1).

Other occupations that have been suggested to be linked with the development of sinonasal cancers include agricultural workers, workers in food manufacturing and preserving, and workers in the textile industry, and in the manufacturing of rubber and plastic products (Leclerc *et al.*, 1997; Luce *et al.*, 2002).

Nasopharyngeal cancers occurring in low-risk populations, including Europe and the US, peak in adolescents and young adults and are associated with Epstein-Barr virus (EBV) infection. The highest risk populations are in the Cantonese region of Southern China and Hong Kong Special Administrative Region, followed by Taiwan, China, the Arctic region, Southeastern Asia, and North Africa. In these high-risk populations, peak incidence is at 50–59 years and the most important risk factors are dietary in association with EBV infection (Yu & Yuan, 2002; IARC, 2012a).

Table 4.2 Other risk factors for nasopharyngeal cancer[a]

Exposure	Reference
Chlorophenol	Zhu *et al.*, (2002), IARC (1999)
Epstein-Barr virus (EBV)	IARC (1997, 2012a)
Ingestion of salted fish and preserved foods during childhood	IARC (2002, 2012c)
Formaldehyde	IARC (1995, 2012d)
Mustard gas	IARC (1987, 2012d)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens except for chlorophenol (2B)

Tobacco smoking is a risk factor for both sinonasal cancer ('t Mannetje *et al.*, 1999; IARC, 2002) and nasopharyngeal cancer, in addition to occupational exposure to formaldehyde or mustard gas (Table 4.2). Squamous cell carcinomas in the nasopharynx have also been linked with exposure to a wood preservative, chlorophenol (Table 4.2; IARC, 1999; Zhu *et al.*, 2002).

It is worth noting that EBV infects almost everyone worldwide but the infection is usually kept dormant by the immune system. Exposure to agents that deregulate the immune system may potentially activate this oncogenic virus (IARC, 2012a).

No published reports were available to the Working Group on genetic susceptibility to development of sinonasal cancers or nasopharyngeal carcinoma associated with exposure to wood or leather dusts.

4.5 Synthesis

Potential mechanisms responsible for the carcinogenicity of wood dust include tissue injury induced by the deposition of wood dust particles in the sinonasal region, impaired ciliary clearance, direct genotoxicity and indirect genotoxicity secondary to chronic inflammation. Wood or leather dusts may also act as carrier for other genotoxic agents (e.g. chromate). There is weak evidence for these mechanisms in cellular assays, short-term animal assays, or assays for genotoxicity using peripheral blood cells or buccal epithelial cells obtained from workers exposed to wood dust.

Workers exposed to wood or leather dusts have increased frequencies of metaplasia and hyperplasia in nasal epithelial biopsies, although these alterations are not considered to be precursor lesions of neoplasia at this organ site. In one study, leather workers also showed increased evidence of dysplasia in nasal biopsies. No mechanistic data were available to the Working Group for leather dust exposure.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of wood dust. Wood dust causes cancer of the nasal cavity and paranasal sinuses and of the nasopharynx.

There is *inadequate evidence* in experimental animals for the carcinogenicity of wood dust.

Wood dust is *carcinogenic to humans (Group 1).*

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LIST OF ABBREVIATIONS

8-h TWA	Eight-hour TWA
8-OH-dG	8-hydroxydeoxyguanine
AAS	atomic absorption spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
AG-AAS	Arsine generation atomic absorption spectrometry
AS3MT	arsenic +3 oxidation state methyltransferase
ASA Register	Finnish Register of Workers Exposed to Carcinogens
As–GSH	arsenic–glutathione
BALF	bronchoalveolar lavage fluid
CARET	Beta-Carotene and Retinol Efficacy Trial
CAREX	CARcinogen EXposure
CAS	Chemical Abstracts Service
CBD	chronic beryllium disease
DMAs	dimethylated arsenic species
DMAV	dimethylarsinic acid
DMBA	7,12-dimethylbenz[α]anthracene
DMMTAV	Dimethylthioarsinic acid
DQ12	uncoated quartz
DSMA, or cacodylic acid	disodium methanearsonate
DWA	Daily weighted average
EBV	Epstein-Barr virus
ECVAM	Centre for the Validation of Alternative Methods
EDAX	energy dispersive analysis of X-rays
ET-AAS	electrothermal atomic absorption spectroscopy
F344	Fisher 344
FBs	Ferruginous bodies
Fpg	formamidopyrimidine-DNA-glycosylase
G6PD	glucose 6-phosphate dehydrogenase
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GC-ECD	gas chromatography-electron capture detection
GF-AAS	graphite furnace atomic absorption spectrometry
GSD	geometric standard deviation
GSH	glutathione
HOBr	hypobromous acid
HOC1	hypochlorous acid
hOGG1	human 8-oxoguanine-DNA-glycosylase
HPV	human papillomavirus

ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
IMA	International Mineralogical Association
IMIS	Integrated Management Information System
ITAC	intestinal-type sinonasal adenocarcinoma
JEM	job–exposure matrix
LEV	local exhaust ventilation
MBDs	methyl-CpG binding domains
MDF	medium-density fibreboard
MGMT	O6-methylguanine-DNA methyltransferase
MIG/MAG-method	Metal Inert Gas-Metal Active Gas
MLHT	malignant lymphomas of the histiocytic type
MMAD	mass median aerodynamic diameter
MMAs	Monomethylated arsenic species
MMAV	monomethylarsonic acid
MnTBAP	manganese(III)meso-tetrakis(4-benzoic acid)porphyrin
MSHA	Mine Safety and Health Administration
MSMA	monosodium methanearsonate
NDEA	N-nitrosodiethylamine
NHANES III	Third National Health and Nutrition Examination Survey
Ni–Cd	nickel–cadmium
NIOSH	National Institute of Occupational Safety and Health
NOES	National Occupation Exposure Survey
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAHs	polyaromatic hydrocarbons
PARP	poly ADP-ribose polymerase
PCP	pentachlorophenol
PD-1	programmed death-1
PMNs	polymorphonuclear leukocytes
PMR	proportionate mortality ratio
RCF-1	refractory ceramic fibres
REL	recommended exposure limit
RLE-6TN	type II lung epithelial cells
RR	relative risk
SHE	Syrian hamster embryo
SiO4	silicate tetrahedron
SIR	standardized incidence ratio
SMR	Standard Mortality Ratio
SV40	simian virus 40
TEM	transmission electron microscopy
TPA	12-O-tetradecanoyl phorbol-13-acetate
TWA	Time-weighted average
UV	ultraviolet
UVR	ultraviolet radiation
XPA	xeroderma pigmentosum group A
XRCC1	X-ray complementing group 1 gene
Zn	zinc

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